Immunosuppressants, Oral
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Prophylaxis Against Organ Rejection			Rheumatoid Arthritis	Refractory Plaque Psoriasis
		Heart	Kidney	Liver		
azathioprine (Azasan®)[1]	Salix		X adjunctive		X	
azathioprine (Imuran®)[2]	generic		X adjunctive		X	
cyclosporine* (Sandimmune®)[3]	Novartis, generic	X adjunctive	X adjunctive	X adjunctive		
cyclosporine, modified (Gengraf®, Neoral®)[4,5]	Abbott, Novartis, generic	X adjunctive	X adjunctive	X adjunctive	X refractory	X
everolimus (Zortress®)[6]	Novartis		X adjunctive*	X adjunctive		
mycophenolate mofetil (CellCept®)[7]	Roche, generic	X adjunctive	X adjunctive	X adjunctive		
mycophenolate sodium (Myfortic®)[8]	Novartis, generic		X adjunctive			
sirolimus† (Rapamune®)[9]	Wyeth, generic		X adjunctive			
tacrolimus (Prograf®)[10]	generic	X adjunctive	X adjunctive	X adjunctive		
tacrolimus extended-release (Astagraf XL®)[11]	Astellas		X adjunctive			
tacrolimus extended-release (Envarsus XR®)[12]	Veloxis		X adjunctive			

Oral immunosuppressants included in this table when used in the setting of organ transplant are rarely utilized as single agents but rather are used in various combinations along with corticosteroids and other appropriate agents based on product labeling, established literature and local protocols.

*Cyclosporine is also available as a 0.05% ophthalmic emulsion for the treatment of xerophthalmia, this formulation and indication will not be included in this review

† Sirolimus (Rapamune) is also approved for the treatment of patients with lymphangioleiomyomatosis (LAM).

OVERVIEW

The ultimate goal of immunosuppressive therapy after organ transplantation is to prevent organ rejection, prolong graft and patient survival by providing an environment of permanent acceptance or tolerance where the new organ is recognized as "self" by the host's immune system. The sequence of events in graft rejection is (1) recognition of donor's histocompatibility differences by the recipient's immune system, (2) recruitment of activated lymphocytes, (3) initiation of immune effector mechanisms, and (4) destruction of the graft. These events can take place at varying rates and may involve differing effects or mechanisms. Therefore, rejection of the transplanted tissue can take place at any time following surgery.

Rejection can be classified as hyperacute, acute cellular, or chronic. Hyperacute rejection may occur when donor-specific antibodies are present in the recipient at the time of transplant. It often occurs within minutes of transplant but may occur anytime within the first 2 weeks following surgery. Alloreactive T lymphocytes that appear in circulation infiltrate the allograft through the vascular endothelium and mediate acute cellular rejection. This type of rejection may occur as early as a few days postoperatively; however, it can occur anytime after transplantation. The process of chronic rejection is poorly understood, although it may simply be a slow form of cellular rejection. The clinical presentation of chronic rejection is dependent on the organ grafted and generally presents as normal organ aging. The onset of chronic rejection is very slow, and the changes in organ function are not usually reversible.

The drugs and dosing used in the maintenance of transplanted organs varies, but the regimens generally follow the same principles. Following induction therapy at the time of surgery, transplant recipients are started on drug regimens that consist of several categories. Antiproliferative agents, such as azathioprine (Azasan, Imuran) and mycophenolate (CellCept, Myfortic), are used as adjunctive therapy. Sirolimus (Rapamune) and everolimus (Zortress) are proliferation inhibitors with mechanisms of action different from that of mycophenolate. They may be used in order to decrease the doses of calcineurin inhibitors (CNI), such as cyclosporine (Gengraf, Neoral, Sandimmune) or tacrolimus (Prograf, Astagraf XL, Envarsus XR), which are typically included in the regimen but can have serious adverse events at higher therapeutic concentrations. The 2009 KDIGO (Kidney Disease Improving Global Outcomes) clinical practice guidelines for the care of kidney transplant recipients recommends using a combination of a CNI and an antiproliferative agent, with or without corticosteroids as initial maintenance immunosuppressive therapy (1B).[13] Further, these guidelines suggest tacrolimus be the first-line CNI used (2A) and that mycophenolate be the first-line antiproliferative agent (2B). The guidelines recommend that if a mammalian target of rapamycin (mTOR) inhibitor such as everolimus or sirolimus is utilized, it should not be started until graft function is established and surgical wounds are healed. The American Association for the Study of Liver Diseases (AASLD) and the American Society of Transplantation have published guidelines for the long term medical management of both adults and pediatric patients following liver transplantation.[14,15] According to these guidelines, there is no standard-of-care designation for choice of immunosuppressive regimen or particular dosing regimen. The choice of immunosuppressive regimen depends a variety of factors including the indication for the transplantation and the risk of drug side effects.

Azathioprine is indicated for the treatment of rheumatoid arthritis (RA), although is rarely used in this setting due to the more recent introduction of tumor necrosis factor inhibitors that are commonly employed in patients who fail to achieve an adequate response with disease-modifying antirheumatic drugs (DMARDs). According to the 2015 American College of Rheumatology guidelines, initial therapy for RA should include early use of a DMARD with methotrexate listed as the preferred initial therapy for most patients with early RA who have active disease.[16] The guidelines state that azathioprine, cyclosporine, minocycline, and gold were considered by the reviewers but were not included in the guidelines for RA based on their infrequent use and lack of new data since 2012.

Cyclosporine has also been used for the treatment of severe, refractory plaque psoriasis in patients unresponsive to other therapies. The American Academy of Dermatology recommends cyclosporine only be considered in adult, nonimmunocompromised patients with severe (extensive or disabling), recalcitrant psoriasis.[17] Recalcitrant is further defined as those patients who have failed to respond to at least one systemic therapy or in patients for whom other systemic therapies are contraindicated or

cannot be tolerated. The American Academy of Dermatology acknowledges that some guidelines suggest the use of cyclosporine in moderate to severe psoriasis and state that cyclosporine efficacy has been observed in erythrodermic psoriasis, generalized pustular psoriasis and palmoplantar psoriasis.

Sirolimus (Rapamune) received FDA approval for the treatment of lymphangioleiomyomatosis (LAM) on May 29, 2015. LAM is a progressive lung disease of women that usually occurs during their childbearing years. LAM affects predominantly the lungs but also the kidneys and lymphatic system. Sirolimus is the first approved treatment that helps to stabilize lung function in some women with LAM.

PHARMACOLOGY[18]

Drug	Mechanism of Action
azathioprine (Azasan/Imuran)	Azathioprine acts as a suppressor of delayed hypersensitivity and cellular cytotoxicity to a greater extent than it acts as a suppressor of antibody responses Azathioprine inhibits purine metabolism; inhibits the synthesis of DNA, RNA, and proteins; interferes with cellular metabolism; and inhibits mitosis
cyclosporine (Sandimmune, Gengraf, Neoral)	Cyclosporine specifically and reversibly inhibits immunocompetent lymphocytes in the G_0 and G_1 phase of the cell cycle The T helper cell is the main target; however, the T-suppressor cell may be targeted as well In addition, cyclosporine inhibits lymphokine production and release
everolimus (Zortress)	Everolimus inhibits antigenic- and interleukin (IL-2 and IL-15)-stimulated activation and proliferation of T- and B-lymphocytes In cells, everolimus binds to FKBP-12 to form an immunosuppressive complex that binds to and inhibits the mammalian target of rapamycin (mTOR), a key regulatory kinase Consequently, subsequent protein synthesis and cell proliferation are inhibited The everolimus:FKBP-12 complex has no effect on calcineurin activity
mycophenolate (CellCept, Myfortic)	Mycophenolate mofetil is a prodrug that is immediately and completely hydrolyzed to the active metabolite, mycophenolate (mycophenolic acid), a reversible and uncompetitive inhibitor of inosine monophosphate dehydrogenase It inhibits the *de novo* synthesis of the guanosine nucleotide without incorporation into DNA and exerts a potent cytostatic effect on B and T lymphocytes
sirolimus (Rapamune)	Sirolimus inhibits T lymphocyte activation and proliferation that occurs in response to antigenic and cytokine stimulation by a unique mechanism Sirolimus also binds to FKBP-12 to generate an immunosuppressive complex that has no effect on calcineurin; this complex binds to and inhibits the activation of mTOR, resulting in suppression of cytokine-driven T cell proliferation and inhibition of the progression from the G_1 to the S phase of the cell cycle
tacrolimus (Prograf, Astagraf XL, Envarsus XR)	Tacrolimus inhibits T lymphocyte activation possibly by binding to an intracellular protein, FKBP-12, forming a complex Calcium, calmodulin, and calcineurin are formed and the phosphatase activity of calcineurin is inhibited; this effect may prevent the dephosphorylation and translocation of activated T cells, a nuclear component thought to initiate gene transcription for the formation of lymphokines

PHARMACOKINETICS[19,20,21,22,23,24,25,26,27,28,29,30,31]

Drug	Half-life (hr)	Metabolites	Excretion (%)	Target Drug Concentrations	
azathioprine (Azasan/Imuran)	5	6-mercaptopurine 6-thioinosinic acid	Hepatic Renal (1–2)	Not measured	
cyclosporine (Sandimmune)	19	--	Biliary Renal (6, 0.1 unchanged)	100–200 ng/mL (may vary depending on specific organ transplanted)	
cyclosporine, modified (Gengraf/Neoral)	8.4	--	Biliary Renal (6, 0.1 unchanged)	100–200 ng/mL (may vary depending on specific organ transplanted)	
everolimus (Zortress)	30	--	Fecal 80 Renal 5	3–8 ng/mL whole blood trough concentrations using LCMSMS	
mycophenolate mofetil (CellCept)	17.9	mycophenolic acid MPA-O-glucuronide MPA-acyl glucuronide	Fecal 6 Renal 93	Not measured	
mycophenolate sodium (Myfortic)	8–16	MPA-O-glucuronide MPA-acyl glucuronide	Renal <60 (3 unchanged)	Not measured	
sirolimus (Rapamune)	57–63 (up to 72 in males)	Hydroxysirolimus Demethylsirolimus hydroxy-demethyl-sirolimus	Fecal 91 Renal 2.2	Adult	Pediatric
				High immunologic risk: 10-15 ng/mL	≥ 13 years old and > 40 kg: 16-24 ng/mL for 12 months, then 12–20 ng/mL thereafter
				Low to moderate immunologic risk: Following cyclosporine withdrawal: 16–24 ng/mL for 12 months, then 12-20 ng/mL thereafter	≥ 13 years old and < 40 kg: 16–24 ng/mL for 12 months, then 12–20 ng/mL thereafter
tacrolimus (Prograf)	11.3	13-demethyl tacrolimus di-demethyl-tacrolimus	Renal <1 unchanged Bile extensive	Adult	Pediatric
				Kidney transplant, Month 1 to 3: 7–20 ng/mL Month 4 to 12: 5–15 ng/mL	--
				Liver transplant, Month 1 to 12: 5–20 ng/mL	Liver transplant, Month 1 to 12: 5–20 ng/mL
				Heart transplant, Month 1 to 3: 10–20 ng/mL ≥ 4 months: 5–15 ng/mL	--

Pharmacokinetics (continued)

Drug	Half-life (hr)	Metabolites	Excretion (%)	Target Drug Concentrations	
tacrolimus extended-release (Astagraf XR)	32–48	13-demethyl tacrolimus 31-demethyl tacrolimus	Fecal 93 Urine: 2	With basiliximab induction without induction	Day 1–60: 5–17 ng/mL Month 3–12: 4–12 ng/mL Day 1–60: 6–20 ng/ml Month 3–12: 6–14 ng/mL
tacrolimus extended release (Envarsus XR)	31 ± 8.1	13-demethyl tacrolimus 31-demethyl tacrolimus	Fecal 93 Urinary: 2	Whole blood trough concentration range of 4 to 11 ng/mL	

Because the rate and extent of absorption of mycophenolate mofetil and mycophenolate sodium delayed-release products are not equal, these products should not be used interchangeably without health care provider supervision.

Because the various cyclosporine products, including some nonproprietary products, are not bioequivalent to each other due to differences in the rate and extent of absorption, these products should not be used interchangeably without health care provided supervision.

Tacrolimus extended-release capsules (Astagraf XL) are not interchangeable with tacrolimus immediate-release capsules or tacrolimus extended release tablets (Envarsus XR)

Patients with malabsorption may have difficulty in achieving therapeutic cyclosporine levels with Sandimmune soft gelatin capsules or oral solution.

CONTRAINDICATIONS/WARNINGS[32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47]

Azathioprine is contraindicated in the treatment of RA in pregnant women. The risk of developing neoplasia is increased dramatically in azathioprine-administered patients with RA who have previously been treated with alkylating agents (cyclophosphamide, chlorambucil, melphalan, or others).

Azathioprine is metabolized to 6-mercaptopurine (6-MP) and then undergoes 2 major inactivation routes. One route is thiol methylation, which is catalyzed by the enzyme thiopurine S-methyltransferase (TPMT) to form an inactive metabolite. TPMT activity is controlled by a genetic polymorphism. Approximately 10% of Caucasians and African-Americans have 1 non-functional TPMT allele and 0.3% of this population has 2 TPMT non-functional alleles. Patients with 1 non-functional TPMT allele (intermediate TPMT activity) may be at increased risk of myelotoxicity at conventional doses of azathioprine. Patients with 2 non-functional TPMT alleles are at an increased risk of developing severe, life-threatening myelotoxicity when receiving conventional doses of azathioprine. Testing for TPMT genotype is recommended in patients who are to receive azathioprine.

Cyclosporine products are contraindicated in psoriasis or RA patients with abnormal renal function, uncontrolled hypertension, or malignancies. Cyclosporine products are also contraindicated if given to psoriasis patients concomitantly with PUVA or UVB, methotrexate, or other immunosuppressive agents, coal tar or radiation therapy due to the risk of fatal malignancies and/or infections.

All immunosuppressants in this category carry warnings, including black box warnings, regarding the risk of development of serious infections, especially for transplant recipients. Fungal, viral, bacterial, and protozoal infections should be treated aggressively as infections may be fatal. Activation of latent viral infections should be monitored. Polyomavirus, especially BK virus, activation may result in serious and sometimes, fatal outcomes. Reduction of immunosuppressant dosage or use of other drugs should be considered as well. Immunosuppressant labeling also contains a black box warning that only

individuals well versed in the management of systemic immunosuppressive therapy who are capable of monitoring these agents appropriately should prescribe them. These agents may also increase the risk of lymphoma or other neoplasias, particularly those of the skin. Patients should be warned to avoid excess ultraviolet light exposure. The increased risk appears related to the intensity and duration of immunosuppression rather than to the use of specific agents.

Azathioprine (Azasan, Imuran) labeling contains an additional black box warning regarding reports of post-transplant lymphoma and hepatosplenic T-cell lymphoma (HSTCL) in patients with inflammatory bowel disease. Azathioprine may cause severe leukopenia, thrombocytopenia, macrocytic anemia, or severe bone marrow depression. These hematologic toxicities are dose-related and seem to be more severe in renal transplant patients who are undergoing organ rejection.

The black box warnings for cyclosporine products reminds practitioners that the bioavailability of cyclosporine (Sandimmune) is not equal to that of cyclosporine; modified (Gengraf, Neoral) and appropriate monitoring should take place if a product change is necessary. Because the absorption of cyclosporine soft gelatin capsules and oral solution can be erratic, prescribers are also warned to monitor cyclosporine concentrations at repeated regular intervals to make sure therapeutic concentrations are maintained.

Cyclosporine products have the potential for thrombocytopenia and microangiopathic hemolytic anemia, hyperkalemia, hyperuricemia, hepatotoxicity, convulsions, encephalopathy, and anaphylaxis. Recommended doses of cyclosporine may cause systemic hypertension and nephrotoxicity. This risk increases as the dose and duration of therapy increases. Monitor renal function during therapy, as renal dysfunction, including structural kidney damage, is a potential adverse effect of cyclosporine. Since cyclosporine may cause hyperkalemia, potassium-sparing diuretics should not be used to treat hypertension.

Everolimus (Zortress) has a black box warning for increased incidence of kidney graft thrombosis, and prescribers are cautioned to use reduced doses of cyclosporine in combination with everolimus to reduce nephrotoxicity. Use of everolimus in heart transplantation is not recommended due to increased mortality. Patients who have hypersensitivity reactions to sirolimus (Rapamune) should not take everolimus.

The use of everolimus has been associated with angioedema, impaired wound healing and fluid accumulation, hyperlipidemia, non-infectious pneumonitis, proteinuria, new onset diabetes mellitus after transplantation, and male infertility. The concomitant use of everolimus with cyclosporine may increase the risk of thrombotic microangiopathy/thrombotic thrombocytopenic purpura/hemolytic uremic syndrome. Monitor hematologic parameters. Everolimus should not be administered earlier than 30 days after liver transplant due to an associated increase in hepatic artery thrombosis reported with mammalian target of rapamycin (mTOR) inhibitors.

Cases of interstitial lung disease (ILD), some reported with pulmonary hypertension, including pulmonary arterial hypertension, have occurred in patients receiving everolimus. Most cases generally resolve on drug interruption; however, fatal cases have occurred. A diagnosis of ILD should be considered in patients presenting with symptoms consistent with infectious pneumonia but not responding to antibiotic therapy and in whom infectious, neoplastic and other non-drug causes have been ruled-out through appropriate investigations.

Mycophenolate (CellCept, Myfortic) labeling contains a black box warning for an increased risk of first trimester pregnancy loss and congenital abnormalities if taken during pregnancy. Patient counseling

and contraception is recommended for women of child bearing potential. If hormonal contraception is utilized (e.g., birth control pill, transdermal patch, vaginal ring, parenteral options), an additional barrier contraceptive method must be used due to the potential for mycophenolate to interfere with the metabolism of these agents.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolic acid (MPA) derivatives in combination with other immunosuppressive agents. Patients receiving mycophenolate may develop severe neutropenia [Absolute neutrophil count (ANC) less than 0.5 × 10^3/mcL]. Patients should be monitored for blood dyscrasias and if they occur, therapy should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately.

Agranulocytosis and cases of pure red cell aplasia (PRCA) have also been reported in patients treated with tacrolimus. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease, or concomitant medications associated with PRCA. If PRCA is diagnosed, discontinuation of tacrolimus or tacrolimus extended-release (ER) should be considered.

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with mycophenolate mofetil and mycophenolate sodium (MMF, MPA CellCept, Myfortic). Hemiparesis, apathy, confusion, cognitive deficiencies, and ataxia were the most frequent clinical features observed. PML may be due to activation of Polyomavirus (e.g., JC virus). The reported cases generally had risk factors for PML, including treatment with immunosuppressant therapies and impairment of immune functions. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms taking mycophenolate mofetil or mycophenolate (CellCept, Myfortic) and consultation with a neurologist should be considered as clinically indicated.

Viral reactivations of hepatitis B (HBV) or hepatitis C (HCV) as well as cytomegalovirus (CMV) have been reported in patients treated with immunosuppressants, including mycophenolate (CellCept, Myfortic). Consideration should be given to reducing immunosuppression in patients who develop evidence of new or reactivated viral infections.

Mycophenolate should be used with caution in patients with active serious digestive system disease. Gastrointestinal bleeding has been observed as well as rare cases of gastrointestinal perforation.

Mycophenolate is an IMPDH (inosine monophosphate dehydrogenase) inhibitor and should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndromes because exacerbated disease symptoms such as gout, tophi, nephrolithiasis or renal disease including renal failure due to the overproduction and accumulation of uric acid may occur.

Sirolimus (Rapamune) carries a black box warning advising that the safety and efficacy of sirolimus in liver and lung transplant patients have not been established; therefore, use is not recommended. In a study in *de novo* liver transplant patients, the combination of sirolimus and tacrolimus (Prograf) was associated with excess mortality and graft loss. Many of these patients had evidence of infection at or near the time of death. In this and another study in *de novo* liver transplant recipients, the use of sirolimus in combination with cyclosporine or tacrolimus was associated with an increased risk of hepatic artery thrombosis (HAT). Most cases of HAT occurred within 30 days post-transplantation and led to graft loss or death. When sirolimus has been used as part of an immunosuppressant regimen for

lung transplant cases, bronchial anastomotic dehiscence, mostly fatal, has been reported. Sirolimus must be protected from light.

The safety and efficacy of sirolimus without concurrent cyclosporine treatment in renal transplant patients have not been adequately studied; therefore, it is not recommended. Sirolimus may increase serum cholesterol and triglyceride concentrations necessitating treatment. Sirolimus has also been associated with angioedema, hypersensitivity reactions, impaired or delayed wound healing, fluid accumulation, renal dysfunction, non-infectious pneumonitis and proteinuria. The concomitant use of sirolimus and a CNI may increase the risk of CNI-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiography (HUS/TTP/TMA).

Tacrolimus (Prograf, Astagraf XL, Envarsus XR) may also cause insulin-dependent post-transplant diabetes mellitus in as many as 11% to 22% of transplant patients. Tacrolimus can also induce nephrotoxicity, which was reported in about 36% to 59% of transplantation patients. To avoid nephrotoxicity, cyclosporine, in particular, should not be used within 24 hours of tacrolimus. Approximately 55% of liver transplant patients developed neurotoxicity including tremor and headache, and other changes in motor function, mental status, and sensory function in 2 randomized studies. Mild to severe hyperkalemia was reported in 8% to 45% of transplant recipients after treatment with tacrolimus.

Tacrolimus has been associated with myocardial hypertrophy, particularly in those with high drug trough concentrations. It is reversible in most cases following dose reduction or discontinuation.

Tacrolimus may prolong the QT/QTc interval and may cause Torsade de Pointes and should be avoided in patients with congenital long QT syndrome. Consideration for obtaining electrocardiograms and monitoring serum electrolytes should be given in patients with congestive heart failure, bradyarrhythmias or those taking certain antiarrhythmic medications or other medicinal products that lead to QT prolongation as well as patients with hypokalemia, hypocalcemia or hypomagnesemia.

Coadministration of tacrolimus (Prograf, Astagraf XL, Envarsus XR) with strong CYP3A4-inhibitors (list not inclusive: grapefruit juice, protease inhibitors, azole antifungals, verapamil, diltiazem, nifedipine, macrolide antibiotics, chloramphenicol) or strong CYP3A4-inducers (list not inclusive: rifampin, rifabutin, phenytoin, carbamazepine, phenobarbital, St. John's Wort) is not recommended without dosing adjustments of tacrolimus and close monitoring of tacrolimus whole blood trough concentrations and tacrolimus-associated adverse reactions. This is especially important with drugs that prolong the QT interval. In such cases monitoring for QT prolongation is also recommended.

The use of live vaccines should be avoided during treatment with any of the agents in this review.

Pure red cell aplasia (PRCA) has been reported in patients treated with tacrolimus.

Tacrolimus has been associated with gastrointestinal perforation, all reported cases have been considered to be a complication of transplant surgery or accompanied by infection, diverticulum or malignant neoplasm.

All of the warnings associated with tacrolimus are applicable to tacrolimus ER.

An additional black box warning for tacrolimus ER is the risk of increased mortality in female liver transplant recipients. A clinical trial involving 471 liver transplant patients randomized to either tacrolimus ER (Astagraf XL) or tacrolimus (Prograf) demonstrated a 10% higher mortality among the 76 female patients (18%) treated with tacrolimus ER (Astagraf XL) compared to the 64 female patients

(8%) treated with tacrolimus at 12 months. Use of tacrolimus ER is not recommended in liver transplantation.

Tacrolimus ER (Astagraf XL) capsules are not interchangeable or substitutable with tacrolimus immediate-release capsules or tacrolimus ER (Envarsus XR) tablets. There have been reports of medication and dispensing errors during post-marketing surveillance. Cases of graft rejection have occurred that may have been related to the medication error and the resulting under-or over-exposure to tacrolimus.

Risk Evaluation and Mitigation Strategy (REMS)[48]

Mycophenolate-containing products (CellCept, Myfortic) REMS requirement consists of a Medication Guide, elements to assure safe use, such as healthcare provider training and communications, and assessments of the REMS.

DRUG INTERACTIONS[49,50,51,52,53,54,55,56,57,58,59,60]

Avoid the concomitant use of azathioprine (Azasan, Imuran) and mercaptopurine due to the potential for severe myelosuppression. Coadministration of azathioprine and any agent, which may affect leukocyte production, should be cautioned as this combination may lead to exaggerated leukopenia, especially in renal transplant patients. Anemia and severe leukopenia are also possible with concomitant use of Angiotensin Converting Enzyme (ACE) inhibitors and azathioprine. Concomitant allopurinol administration requires azathioprine dose reduction by 66% to 75%. Cases of severe pancytopenia have been reported in Hepatitis C patients receiving ribavirin in conjunction with azathioprine. Patients receiving this combination should have complete blood counts monitored weekly for the first month, twice monthly for the second and third months and then monthly thereafter. There is *in vitro* evidence that aminosalicylate derivatives (e.g., sulfasalazine, mesalazine) inhibit the TPMT enzyme and therefore the use of these agents with azathioprine is cautioned.

Azathioprine may inhibit the anticoagulant effect of warfarin.

Concomitant use of cyclosporine products (Sandimmune, Gengraf, Neoral) with other nephrotoxic drugs, including non steroid antiinflammatory drugs (NSAIDs), may potentiate renal dysfunction, especially in dehydrated patients. Because cyclosporine is extensively eliminated by cytochrome P450 3A4 and P-glycoprotein (P-gp), monitoring of circulating cyclosporine concentrations and appropriate dosage adjustments are essential when used concomitantly with other drugs that are inducers or inhibitors of CYP3A4 or P-gp. Drugs that are known to increase cyclosporine concentrations include (list not all-inclusive): calcium channel blockers (diltiazem, nicardipine, verapamil), azole antifungals, macrolide antibiotics, quinupristin/dalfopristin, methylprednisolone, allopurinol, amiodarone, bromocriptine, colchicine, danazol, protease inhibitors, imatinib, metoclopramide, nefazodone and oral contraceptives. Grapefruit juice is also known to increase blood concentrations of cyclosporine. Drugs or dietary supplements known to decrease cyclosporine concentrations include (list not all-inclusive): rifampin, carbamazepine, phenobarbital, phenytoin, bosentan, octreotide, terbinafine, ticlopidine and St. John's Wort. In RA patients coadministered diclofenac or methotrexate with cyclosporine, the AUC of diclofenac and methotrexate each was significantly increased. Orlistat decreases cyclosporine absorption and its use should be avoided in patients receiving oral cyclosporine. Frequent gingival hyperplasia has been reported with the concurrent administration of nifedipine and cyclosporine.

Potassium-sparing diuretics should not be used in conjunction with cyclosporine because hyperkalemia can occur. Caution is also advised when cyclosporine is coadministered with potassium-sparing drugs such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists (ARBs).

Cyclosporine itself is also an inhibitor of CYP3A4 and of PgP, and therefore, may increase plasma concentrations of co-administered medications that are substrates for these metabolic pathways. Cyclosporine may decrease the clearance of (list not all-inclusive): digoxin, colchicine, ambrisentan, prednisolone, HMG-CoA reductase inhibitors (statins), aliskiren, repaglinide, NSAIDs, sirolimus, and etoposide.

Coadministration of dabigatran with cyclosporine should be avoided due to the potential for cyclosporine to result in increased dabigatran concentrations secondary to the P-gp inhibitory activity of cyclosporine.

CYP3A4 and P-glycoprotein (P-gp) are the primary elimination pathways of everolimus (Zortress), so concurrent therapy with potent inducers or inhibitors of CYP3As or P-gp may affect blood concentrations of everolimus. This includes cyclosporine, a 3A4 inhibitor with which everolimus may be administered, according to the indication. Everolimus itself may inhibit 3A4 and 2D6 enzymes. Coadministration of everolimus with depot octreotide has been shown to increase octreotide concentrations by 50%.

Mycophenolate products (CellCept, Myfortic) should not be given with azathioprine because these agents all work to inhibit purine metabolism and could potentially cause bone marrow suppression. Mycophenolate concentrations may be decreased by antacids; therefore, do not administer concurrently.

Coadministration of PPIs (e.g., lansoprazole, pantoprazole) to patients receiving CellCept brand of mycophenolate has been reported to reduce mycophenolic acid (MPA) exposure by approximately 30% in patients; maximum concentration was decreased by 30% to 70%. This may possibly be due to decreased MPA solubility at an increased gastric pH. Although clinical relevance has not been established, PPIs should be used with caution when coadministered.

Mycophenolate is not recommended to be coadministered with cholestyramine or other agents that may interfere with enterohepatic recirculation. MPA exposure was decreased by as much as 40%. Cyclosporine also interrupts the enterohepatic recirculation of MPA, while tacrolimus does not interfere with this process. When MPA is administered concomitantly with cyclosporine or tacrolimus, patients should be monitored for MPA adverse events and have their dose of MPA reduced, if needed.

It is recommended that calcium free phosphate binders, such as sevelamer, are administered 2 hours after mycophenolate mofetil (CellCept) dose to minimize the impact on the absorption of MPA. A 67% reduction in MPA exposure was reported with concomitant administration of mycophenolate mofetil and rifampin; concurrent use is not recommended.

Rifampin should not be given concomitantly with MPA unless the benefit outweighs the risk of decreased exposure to MPA. The combination of metronidazole and norfloxacin reduced MPA exposure by one-third, and therefore, this combination is not recommended to be given concomitantly with MPA.

Because sirolimus is known to be a substrate for cytochrome CYP 3A4 and P-glycoprotein (P-gp), coadministration of sirolimus with strong inhibitors or inducers of CYP3A4 and/or P-gp is not recommended.

Patients with renal impairment who are receiving mycophenolate mofetil concurrently with ganciclovir or valganciclovir should be monitored closely for adverse reactions due to competition for tubular secretion which can increase the concentrations of both drugs.

Mycophenolate mofetil is not recommended to be administered with norfloxacin or metronidazole due to a reduction in mycophenolate concentrations.

Oral contraceptives should used with caution in patients taking mycophenolate products and additional barrier contraceptive methods must be used.

To prevent an additive or synergistic impairment of renal function, tacrolimus (Prograf, Astagraf XL, Envarsus XR) should be coadministered cautiously with other agents that may cause renal impairment, such as aminoglycosides, amphotericin B, and cisplatin. Tacrolimus is primarily metabolized by the CYP3A enzyme systems; therefore, substances known to inhibit these enzymes may decrease metabolism or increase bioavailability and drugs known to induce these enzyme systems may result in an increased metabolism or decreased bioavailability of tacrolimus. Coadministration of tacrolimus with strong CYP3A4-inhibitors (e.g., grapefruit juice, protease inhibitors, such as ritonavir, nelfinavir, telaprevir, and boceprevir, azole antifungals, calcium channel blockers, such as verapamil, diltiazem, nifedipine and nicardipine, macrolide antibiotics, chloramphenicol, cimetidine, amiodarone, bromocriptine, nefazodone, metoclopramide, danazol, ethinyl estradiol and methylprednisolone) or strong CYP3A4-inducers (e.g., rifampin, rifabutin, phenytoin, carbamazepine, phenobarbital, or St. John's wort) is not recommended without dosing adjustments of tacrolimus and close monitoring of tacrolimus whole blood trough concentrations and tacrolimus-associated adverse reactions. This is especially important with drugs that prolong the QT interval, such as protease inhibitors and some antifungal agents. In such cases, monitoring for QT prolongation is also recommended. When voriconazole or posaconazole is initiated in patients already taking tacrolimus, the tacrolimus dose should be reduced to one-third of the original dose and subsequent dosing be based on monitoring of tacrolimus whole blood trough concentrations. Coadministration of magnesium and aluminum hydroxide antacids also increase tacrolimus concentrations and monitoring of tacrolimus whole blood concentrations are recommended when these agents are used concomitantly with tacrolimus.

Lansoprazole and omeprazole may compete with tacrolimus for metabolism through the CYP3A4 system and may substantially increase tacrolimus whole blood concentrations.

Consumption of alcohol with tacrolimus ER (Astagraf XL, Envarsus XR) may increase the rate of release or alter the pharmacokinetic properties of tacrolimus, and therefore, alcoholic beverages should not be consumed with tacrolimus ER (Astagraf XL, Envarsus XR).

The use of live attenuated vaccines should be avoided when possible in patients receiving any oral immunosuppressant and vaccination may be less effective in patients receiving immunosuppressive therapy.

ADVERSE EFFECTS[61,62,63,64,65,66,67,68,69,70]

Drug	Headache	Nausea	Vomiting	Diarrhea	Rash	Tremor	Liver toxicity	Other common effects
azathioprine (Azasan, Imuran)	nr	reported	reported	reported	reported	nr	reported	leukopenia, thrombocytopenia
cyclosporine* (Sandimmune)	2–15	2–10	2–10	3–8	nr	12–55	4–7	gum hyperplasia, hypertension, renal dysfunction, hirsutism
everolimus (Zortress)	18	29	15	19	1–10	8	1–10	constipation, peripheral edema, anemia
mycophenolate mofetil (CellCept)	16.1–54.3	19.9–54.5	32.9–33.9	31–51.3	22.1	24.2–33.9	24.9	leukopenia, anemia, infection
mycophenolate sodium (Myfortic)	3–20	24.5–29.1	23	21.4–23.5	3–20	3–20	nr	leukopenia, anemia, infection
sirolimus (Rapamune)	34	25–31	nr	25–35	10–20	nr	nr	peripheral edema, hypertension, lipid abnormalities
tacrolimus (Prograf)	37–64	32–46	14–27	37–72	10–24	48–56	6–36	hypertension, abnormal renal function, insomnia
tacrolimus extended-release† (Astagraf XL)	12 (10)	15 (13)	13 (13)	27 (31)	nr	18 (17)	nr	new onset diabetes, infections, constipation
tacrolimus extended-release† (Envarsus XR)	9 (7)	nr	nr	14 (9)	nr	nr	nr	new onset diabetes, increased blood creatinine, infections nasopharyngitis, , peripheral edema, hypertension

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

The adverse event data presented here indicates occurrence in transplant (renal, hepatic, cardiac) patients only.

* The package inserts for Gengraf and Neoral reference the adverse event data from studies using Sandimmune.

† The control arm for the Astagraf XL and the Envarsus XR studies were tacrolimus immediate-release (Prograf).

SPECIAL POPULATIONS[71,72,73,74,75,76,77,78,79,80,81,82]

Pediatrics

Safety and efficacy of azathioprine (Azasan, Imuran) and everolimus (Zortress) have not been established in the pediatric population.

Cyclosporine (Sandimmune) has been given to patients as young as 6 months of age without unusual adverse effects; however, there are no adequate, well-controlled studies in children. Cyclosporine, modified (Gengraf, Neoral) has been given to transplant recipients as young as 1 year of age without unusual adverse effects. Cyclosporine whole blood concentrations should be measured and dosages adjusted accordingly. The safety and efficacy of these products have not been established in children less than 18 years old with juvenile RA or psoriasis.

Safety and efficacy of mycophenolate mofetil (CellCept) have not been established in children receiving heart or liver transplants. Based on pharmacokinetic and safety data in pediatric patients after renal transplantation, the recommended dose of mycophenolate mofetil oral suspension is 600 mg/m^2 twice daily (up to a maximum of 1 gram twice daily.) Mycophenolate sodium (Myfortic) has established safety and efficacy in patients 5 to 16 years old who are stable renal transplant recipients. Pediatric doses for patients with a body surface area (BSA) less than 1.19 m^2 cannot be accurately administered using the currently available formulations of mycophenolate sodium (Myfortic) tablets.

Safety and efficacy of sirolimus (Rapamune) for prophylaxis of organ rejection in renal transplantation have not been established in children younger than 13 years of age or in children younger than 18 who are considered to be at high immunologic risk. Safety and efficacy of sirolimus (Rapamune) in lymphangioleiomyomatosis patients less than 18 years have not been established.

Safety and efficacy of tacrolimus (Prograf) in pediatric kidney or heart transplant patients have not been established. There is limited data on the use of tacrolimus (Prograf) in pediatric liver transplantation. However, tacrolimus use after pediatric liver transplantation has been successful. Pediatric liver transplant patients generally required higher doses of tacrolimus to maintain blood trough concentrations of tacrolimus similar to adult patients. The safety and efficacy of tacrolimus ER (Astagraf XL, Envarsus XR) in pediatric kidney transplant patients less than 16 years of age has not been established.

Pregnancy

Azathioprine can cause fetal harm when administered to pregnant women; therefore, azathioprine has been labeled Pregnancy Category D.

Mycophenolate products are Pregnancy Category D. While there are no adequate, well-controlled studies in pregnant women, the use of mycophenolate is associated with an increased risk of first trimester miscarriage and congenital malformations such as external ear and facial abnormalities and anomalies of the distal limbs, heart, esophagus, and kidney.

Cyclosporine products, everolimus, sirolimus, and tacrolimus have been labeled Pregnancy Category C.

Renal Impairment

The dose of azathioprine should be decreased for moderate to severe renal failure.

Patients with renal impairment should receive doses of tacrolimus at the lowest value of the recommended initial dosing range and renal function should be monitored. Doses of everolimus (Zortress) in patients with moderate or severe renal impairment should be reduced by one half initially.

Hepatic Impairment

Patients taking everolimus who have moderate hepatic impairment should decrease the everolimus dose by half. There is no information available for patients with severe hepatic impairment.

For patients with mild or moderate liver impairment, it is recommended that the maintenance dosage of sirolimus be reduced by approximately one-third, and the maintenance dose should be reduced by one-half in those with severe liver impairment. However, it is not necessary to reduce the loading dose of sirolimus.

Patients with hepatic impairment should receive doses of tacrolimus at the lowest value of the recommended initial dosing range.

Race

The data in kidney transplant patients indicate that African- American patients required a higher dose of tacrolimus (Prograf) and tacrolimus ER (Astagraf XL, Envarsus XR) to attain comparable trough concentrations compared to Caucasian patients. In addition African-American and Hispanic kidney transplant patients are at an increased risk of new onset diabetes after transplantation and on tacrolimus therapy.

DOSAGES[83,84,85,86,87,88,89,90,91,92,93,94]

Drug	Initial Dose	Maintenance Dose	Pediatric Dose	Availability
azathioprine (Azasan)	Transplant: 3–5 mg/kg once daily RA: 1 mg/kg/day (50–100 mg) once or twice daily	Transplant: 1–3 mg/kg once daily RA: 1–2.5 mg/kg/day once or twice daily	--	75, 100 mg tablets
azathioprine (Imuran)	Transplant: 3–5 mg/kg once daily RA: 1 mg/kg/day (50–100 mg) once or twice daily	Transplant: 1–3 mg/kg once daily RA: 1–2.5 mg/kg/day once or twice daily	--	50 mg tablet
cyclosporine (Sandimmune)	15 mg/kg as a single dose 4 to 12 hours prior to transplant 14–18 mg/kg once daily for 1 to 2 weeks	Transplant: 5–10 mg/kg/day once daily; monitor whole blood trough levels with approximate range of 100–200 ng/mL	Same as adult, may require higher doses	100 mg/mL solution 25, 100 mg soft gelatin capsules
cyclosporine, modified (Gengraf, Neoral)	Transplant: 15 mg/kg divided twice daily 4 to 12 hours prior to or immediately post transplant	Transplant: 5–10 mg/kg/day; divided twice daily, monitor whole blood trough levels with approximate range of 100–200 ng/mL	Same as adult	25, 50 (generic only), 100 mg capsules (Gengraf) 25, 100 mg soft gelatin capsules (Neoral) 100 mg/mL solution
	Psoriasis / RA: 2.5 mg/kg divided twice daily	Psoriasis / RA: 2.5–4 mg/kg divided twice daily	--	
everolimus (Zortress)	Kidney: 0.75 mg twice daily at the same time as cyclosporine Liver: 1 mg twice daily started at least 30 days post transplant at same time as tacrolimus	Adjusted to maintain a trough whole blood concentration of 3–8 ng/mL using an LCMSMS assay	--	0.25, 0.5, 0.75 mg tablets
mycophenolate mofetil (CellCept)	--	Renal transplant: 1 gram twice daily	Renal transplant: 600 mg/m^2 twice daily (maximum 2 grams daily)	200 mg/mL powder for suspension 250 mg capsule 500 mg tablet
		Cardiac transplant: 1.5 grams twice daily	--	
mycophenolate mofetil (CellCept)		Hepatic transplant: 1.5 grams twice daily	--	

Dosages (continued)

Drug	Initial Dose	Maintenance Dose	Pediatric Dose		Availability
mycophenolate sodium (Myfortic)	--	720 mg twice daily (empty stomach)	>5 years of age who are at least 6 months post kidney transplant: 400 mg/m^2 twice daily (maximum 720 mg twice daily)		180, 360 mg delayed release tablets
sirolimus (Rapamune)	High immunologic risk: Up to 15 mg loading dose then 5 mg daily in combination with cyclosporine and corticosteroids for at least 12 months	High immunologic risk: Adjust to a trough concentration of 10–15 ng/mL	--		1 mg/mL solution 0.5, 1, 2 mg tablets
	Low to moderate immunologic risk: 6 mg on day 1; then 2 mg daily in combination with cyclosporine and corticosteroids for 2 to 4 months	Low to moderate immunologic risk: Following cyclosporine withdrawal, adjust to trough concentration of 16–24 ng/mL for 12 months then 12–20 ng/mL thereafter	≥ 13 years old and > 40 kg: Same as adult	Adjust to trough level of 16–24 ng/mL for 12 months after cyclosporine withdrawal, then 12–20 ng/mL thereafter	
			≥ 13 years old and < 40 kg: 3 mg/m^2 x 1 then 1 mg/m^2/day	Adjust to trough level of 16–24 ng/mL for 12 months then 12–20 ng/mL thereafter	
	Lymphangioleiomyomatosis: initially 2 mg/day	Measure whole blood trough concentrations in 10–20 days with dosage adjustment to maintain concentration between 5–15 ng/mL	--		

Dosages (continued)

Drug	Initial Dose	Maintenance Dose	Pediatric Dose		Availability
tacrolimus (Prograf)	Kidney transplant: 0.2 mg/kg/day divided twice daily (in combination with azathioprine) 0.1 mg/kg/day (in combinations with MPA)	Kidney transplant in combination with azathioprine: Month 1 to 3: dose to a trough concentration of 7–20 ng/mL Month 4 to 12: dose to a trough concentration of 5–15 ng/mL Kidney transplant in combination with MPA month 1–12 dose to a trough concentration of 4–11 ng/mL	--		0.5, 1, 5 mg capsules
	Liver transplant: 0.1–0.15 mg/kg/day divided twice daily	Liver transplant: Month 1–12: dose to a trough concentration of 5–20 ng/mL	Liver transplant: 0.15–0.2 mg/kg/day divided twice daily	Liver transplant: Month 1 to 12: Dose to a trough concentration of 5–20 ng/mL	
	Heart transplant: 0.075 mg/kg/day divided twice daily	Heart transplant: Month 1 to 3: Dose to a trough concentration of 10–20 ng/mL ≥ Month 4: Dose to a trough concentration of 5–15 ng/mL	--		
tacrolimus extended-release (Astagraf XL)	With basiliximab induction: 0.15 to 0.2 mg/kg/day prior to reperfusion or within 48 hours of complement of transplant procedure	During month 1: dose trough concentrations to 7 to 15 ng/mL Months 2 to 6: dose to 5 to 15 ng/mL > 6 months: dose to 5 to 10 ng/mL	-		0.5, 1, and 5 mg extended-release capsules
	Without induction: pre-operative: 0.1 mg/kg/day	Post-operative: 0.2 mg/kg/day Dose to trough concentrations: During month 1: dose to 10 to 15 ng/mL; Months 2 to 6: dose to 5 to 15 ng/mL > 6 months: dose to 5 to 10 ng/mL			

Dosages (continued)

Drug	Initial Dose	Maintenance Dose	Pediatric Dose	Availability
tacrolimus, extended release (Envarsus XR)	To convert from a tacrolimus, immediate-release (IR) product, give 80% of the total daily dose of the tacrolimus IR product	Adjust dose to achieve target whole blood trough concentration ranges of 4–11 ng/mL	-	0.75, 1, 4 mg extended-release tablets

Many immunosuppressive protocols require combinations of immunosuppressants with or without the addition of corticosteroids; please refer to product labeling for recommended combination regimens.

Do not crush, chew, or cut everolimus (Zortress), mycophenolate (CellCept, Myfortic), or sirolimus (Rapamune) tablets. Do not open mycophenolate (CellCept) capsules.

TPMT phenotype testing is recommended for patients receiving azathioprine.

Cyclosporine (Sandimmune) solution can be made more palatable by diluting it with milk, chocolate milk, or orange juice at room temperature. Cyclosporine (Gengraf, Neoral) solution can be made more palatable by diluting it with apple juice or orange juice at room temperature. Sirolimus solution should be diluted with water or orange juice before administering.

Sirolimus (Rapamune) oral solution must be protected from light.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by the manufacturers. The search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Due to the large number of studies identified for the immunosuppressants, this review focuses on head-to-head trials meant to determine safety or efficacy for FDA-approved indications only. This review is not meant to encompass all trials involving the use of immunosuppressants, such as the benefit of steroid-free regimens, the timing of initiating calcineurin inhibitors or possible calcineurin inhibitor-sparing regimens . Many of the trials performed with these agents are open-label trials due to the need for therapeutic concentration monitoring.

Cardiac Transplant

cyclosporine (Sandimmune) versus tacrolimus (Prograf)

A single-center, randomized, prospective, open-label study was conducted to investigate whether trough concentration-adjusted mycophenolate mofetil is more efficacious in combination with tacrolimus or cyclosporine and to investigate the impact of either drug on mycophenolate mofetil dosage.[95] Immunosuppressive therapy consisted of tacrolimus (n=30) dosed to a target blood trough concentration of 10 to 15 ng/mL or cyclosporine (n=30) dosed to a target blood trough concentration of 100 to 300 ng/mL in combination with mycophenolate mofetil dosed to a target blood trough concentration of 1.5 to 4 mg/mL and corticosteroids. Investigators tracked acute rejection episodes (ARE), survival data, and adverse events. No difference was seen between the groups in baseline characteristics. Corticosteroids were withdrawn within 6 months of cardiac transplant in all patients. The tacrolimus-treated patients had a lower incidence of ARE per 100 patient days compared to cyclosporine (0.03 versus 0.15; p=0.00007). However, overall patient survival during follow-up was similar (93% versus 90%) between the groups. Participants in the tacrolimus group required a lower mycophenolate mofetil dose to achieve the targeted blood concentrations. After 2 years, the mean graft vessel disease score was 1.85 ± 3.18 in the tacrolimus group versus 3.95 ± 4.8 in the cyclosporine group (p=0.08). A 10-year follow-up of this group of patients was published in 2013.[96] Survival for the tacrolimus plus mycophenolate mofetil (TAC/MMF) group was 96.7% at 1 year, 80% at 5 years and 66.7% at 10 years. Survival in the cyclosporine plus mycophenolate mofetil group (CsA/MMF) was 90% at 1 year, 88.3% at 5 years, and 80% at 10 years, none of these differences were statistically significantly different. Freedom from acute rejection episodes (ARE) was significantly higher in the TAC/MMF group (65.5%) versus the CsA/MMF group (21.7%; p=0.004). Freedom from cardiac allograft vasculopathy (CAV) after 5 and 10 years was 64% and 45.8% in the in the TAC/MMF group compared to 36% (p=0.085) and 8% (p=0.003) in the CsA/MMF group. There were no differences between the groups with regard to coronary angioplasty or stenting, renal dysfunction, diabetes mellitus, CMV infections, or malignancies.

The efficacy and safety of tacrolimus and cyclosporine were compared using 73 adult heart transplant patients in a single-center, prospective, randomized, open-label clinical trial.[97] At the time of transplantation, patients were randomly assigned to receive either tacrolimus (n=43) or cyclosporine (n=30). Ten tacrolimus-treated patients received the drug intravenously in the perioperative period, and all other patients received oral tacrolimus only. The mean follow-up was 27 months. The 2 groups had similar patient survival rates (tacrolimus 83%, cyclosporine 81%). Fewer tacrolimus-treated patients (79%) experienced acute rejection when compared to cyclosporine-treated patients (100%, p=NS). The 2 groups were also similar with regard to the number of infections, rate of dialysis, and insulin requirements; however, the proportion of patients requiring multiple antihypertensives was lower in the tacrolimus group (12.5% versus 50% at month 6; p=0.025).

Patients were randomized in a 2:1 fashion to either oral tacrolimus (n=54) or cyclosporine (n=28).[98] The 2 groups had similar rejection and survival rates at 1 year. Kaplan-Meier estimates showed a freedom from rejection of 26.3% for the tacrolimus-treated participants and 18.5% for the cyclosporine-treated participants (p=0.444). Survival rates were 79.6% in the tacrolimus arm and 92.9% in the cyclosporine arm (p=0.125). At 3 of the 5 centers, patients were treated with antithymocyte globulin during the immediate postoperative period. Acute rejection-free rates were 49.2% and 26.7% for tacrolimus and cyclosporine, respectively (p=0.08); for those treated with thymoglobulin, rejection-free rates were

7.1% and 8.3% (p=0.965). Patient survival rates were 84.6% and 93.3% (p=0.382) versus 75% and 92.3% (p=0.243). No significant differences were found between the groups in the overall rates of infection, impaired renal function (31.5% versus 21.4%), or glucose intolerance (7% versus 4.3%). Fewer patients receiving tacrolimus needed antihypertensive therapy (59.5% versus 87.5%; p=0.025).

Cardiac transplant recipients (n=95) were randomized at a single center to either open-label cyclosporine or tacrolimus and were followed to determine the rate of cytomegalovirus (CMV) infection in each group.[99] All patients at highest risk of developing CMV (CMV recipients receiving CMV positive organs) received valganciclovir prophylaxis. CMV infection was considered as the detection of an increased viral load and/or the presence of CMV in histological samples, regardless of clinical symptoms. The rate of CMV infection overall (not just in highest risk patients) was higher in patients treated with cyclosporine than in those treated with tacrolimus (45.1% versus 15.9%; p=0.002). The group of patients treated with cyclosporine had a shorter mean survival time free from CMV infection than patients treated with tacrolimus (900 days versus 1,440 days, p=0.001).

The incidence of obesity in cardiac transplant recipients was studied in 101 heart transplant recipients who were randomly assigned to either cyclosporine or tacrolimus.[100] At baseline there was no difference in weight between the 2 groups. Obesity was defined as a body mass index of ≥ 25 m^2. One year after heart transplant, the mean weight gain was 6.9 ± 11 kg in the cyclosporine group compared to a minimal weight loss of 0.03 ± 14 kg in the tacrolimus group (p=0.008). Multivariate analysis revealed that only cyclosporine treatment was an independent predictor of obesity 1 year after heart transplant (odds ratio [OR], 3.84; 95% CI, 1.04 to 14.21; p=0.01).

cyclosporine, modified (Gengraf/Neoral) versus tacrolimus (Prograf)

Tacrolimus (n=157) was compared to cyclosporine, modified (n=157), each in combination with azathioprine and corticosteroids, in a randomized controlled clinical trial of newly transplanted heart recipients.[101] Acute rejection episodes were assessed by protocol biopsies, which underwent local and blinded central evaluation. At 18 months, patient and graft survival was 92.9% in the tacrolimus-treated group compared to 89.8% in the cyclosporine-treated group. The incidence of first biopsy-proven acute rejection of grade ≥ 1B at month 6, the primary end point was 54% in the tacrolimus arm versus 66.4% in the cyclosporine arm (p=0.029). The incidence of first biopsy-proven acute rejection of grade ≥ 3A at month 6 was 28% in the tacrolimus group and 42% in the cyclosporine group (p=0.013). Significant differences (p≤0.05) were seen between the groups for adverse events, such as new-onset diabetes mellitus (20.3% versus 10.5%), post-transplant arterial hypertension (65.7% versus 77.7%), and dyslipidemia (28.7% versus 40.1%) for tacrolimus versus cyclosporine, respectively.

Heart transplant patients were randomized to receive either tacrolimus (n=33) or cyclosporine, modified (n=34), each in combination with corticosteroids and azathioprine, without induction, in a 5-year follow-up study.[102] Endpoints included survival, Grade ≥ 3A or treated rejection, angiographic cardiac allograft vasculopathy, renal dysfunction, use of 2 or more antihypertensive medications, incidence of diabetes, and lipid concentrations. Significant differences were seen only for the tacrolimus-treated arm: lower 5-year mean triglyceride concentrations (97 ± 34 versus 172 ± 103 mg/dL; p=0.011) and average serum creatinine concentrations (1.2 ± 0.5 mg/dL versus 1.5 ± 0.4 mg/dL; p=0.044). The tacrolimus-treated arm showed a trend toward fewer patients requiring 2 or more antihypertensive drugs; however, this did not reach statistical significance.

A prospective, open-label, multicenter, 12-month study randomized 85 cardiac transplant recipients to receive either tacrolimus-based (n=39) or cyclosporine-based (n=46) immunosuppression.[103] Fifteen

patients (18%) were given peri-operative muromonab (Orthoclone, OKT3) due to pre-transplant renal dysfunction, to delay treatment with tacrolimus or cyclosporine. All patients received a triple-drug protocol with identical adjunctive immunosuppressant agents. Endomyocardial biopsies were performed at weeks 1, 2, 3, 4, 6, 8, 10, 12, 24, and 52. Patients were mostly male (87%), Caucasian (90%), had a mean age of 54 years, and primary diagnoses of coronary artery disease (55%), and idiopathic dilated cardiomyopathy (41%). Patient and allograft survival were not different between the treatment groups. Probability and overall incidence of each grade of rejection, whether treated or not, and the types of treatment required did not differ between the groups. At baseline and through 12 months of follow-up, serum cholesterol concentrations were higher in the cyclosporine group at 3, 6, and 12 months (239 versus 205 mg/dL, 246 versus 191 mg/dL, 212 versus 186 mg/dL, respectively; $p \leq 0.001$). No significant differences were seen in renal function, hyperglycemia, hypomagnesemia, or hyperkalemia during the first 12 months. More cyclosporine-treated patients developed new-onset hypertension requiring drug therapy (71% versus 48%; p=0.05). The incidence of infection was similar for the 2 groups.

Hepatic Transplant

cyclosporine versus tacrolimus (Prograf)

An open-label, multicenter trial randomized 478 adults and 51 children (≤ 12 years of age) to receive tacrolimus (n=263) or cyclosporine (n=266) following hepatic transplantation.[104] Participants were followed for 1-year post-transplant, with primary endpoints of 1-year patient and graft survival. The secondary endpoints were the incidence of acute rejection, corticosteroid-resistant rejection, and refractory rejection, defined as continued rejection after 2 courses of corticosteroids and an intravenous course of muromonab. A Kaplan-Meier analysis showed patient-survival rates at day 360 of 88% for both the tacrolimus and cyclosporine groups (p=0.85), and graft-survival rates of 82% and 79%, respectively (p=0.55). One hundred fifty-four patients in the tacrolimus arm and 173 patients in the cyclosporine arm experienced acute rejection (p≤0.002), and 43 patients in the tacrolimus arm and 82 patients in the cyclosporine arm experienced corticosteroid-resistant rejection (p≤0.001). In addition, refractory rejection occurred in 6 and 32 patients, respectively (p≤0.001). Thirty-seven patients in the tacrolimus arm and 13 patients in the cyclosporine arm discontinued the study due to adverse events, primarily nephrotoxicity and neurotoxicity (p≤0.001).

A total of 529 liver transplant patients participated in a one-year, randomized, multicenter study with a 4-year follow-up extension that compared the safety and efficacy of tacrolimus (n=263) to cyclosporine (n=266).[105] Participants were evaluated at 3-month intervals to determine patient and graft survival rates, incidence of adverse events, and changes in laboratory and clinical profiles. Overall, patient and graft survival rates were comparable between the 2 groups (tacrolimus 79% and 71.8%; cyclosporine 73.1% and 66.4%, respectively). Hepatitis C-positive patients had improved survival with tacrolimus (78.9% tacrolimus group versus 60.5% cyclosporine group; p=0.041). The 2 groups had comparable incidences of late acute rejection, late steroid-resistant rejection and death or graft loss related to rejection. The safety profiles of both treatments were comparable.

The Randomized Evaluation of Fibrosis (REFINE) study was an open-label prospective, randomized, multicenter study.[106] Adult patients (n=356) who had received a liver transplant for hepatitis C virus (HCV) cirrhosis were randomized to cyclosporine or tacrolimus-based regimens. Patients then entered a 12-month treatment phase, with a follow-up assessment at 24 months posttransplant. The primary endpoint was the rate of fibrosis stage ≥ 2 using Ishak-Knodell scoring by 12 months after liver

transplantation. A total of 71.6% of patients randomized to cyclosporine, compared to 67.5% of patients randomized to tacrolimus had fibrosis score ≥ 2 at month 12 (OR, 1.11; 95% CI, 0.56 to 2.21; p=0.759). Similarly, no significant between-group difference occurred at month 24 (OR, 1.15; 95% CI, 0.47 to 2.8; p=0.767) in these patients. However, in the subset of patients who did not receive corticosteroids, a fibrosis score ≥ 2 was significantly less frequent with cyclosporine versus tacrolimus at month 12 (18.9% versus 42.1%; p=0.029).

cyclosporine, modified (Gengraf/Neoral) versus tacrolimus (Prograf)

A prospective, randomized, intent-to-treat, 4-year follow-up trial comparing cyclosporine, modified (n=50) to tacrolimus (n=49) was conducted to evaluate a multidrug approach that would reduce both early and long-term morbidity related to immunosuppression post-hepatic transplant without compromising efficacy.[107] The primary endpoints were rejection and infection, and the secondary endpoints were liver function, renal function, bone marrow function, cardiovascular risk factors, and the recurrence of hepatitis C. Study treatment was started on postoperative day 2 with mycophenolate mofetil. All patients received an identical steroid taper. Forty-six cyclosporine, modified patients and 44 tacrolimus patients completed the full 4 years of follow-up. The overall patient survival rate was 93%, and the overall graft survival rate was 89%. There were no significant differences seen between the study groups in 4-year patient survival (cyclosporine, modified 96% versus tacrolimus 90%; p=NS), graft survival (cyclosporine, modified, 90% versus tacrolimus, 88%; p=NS), or rejection (cyclosporine, modified 34% versus tacrolimus 24%; p=0.28). There were no differences in infection rates. For patients with hepatitis C (n=37), there were also no differences in viral titers or Knodell biopsy scores; however, in the tacrolimus-treated patients, there was a lower rejection rate (p=0.0097) and a lower rate of hepatitis C recurrence (p=0.05). No difference was seen in the percent of patients weaned off steroids after 4 years or in the incidence of diabetes mellitus and hypertension. More patients in the cyclosporine, modified group had a twofold increase in creatinine when compared to the tacrolimus group (63% versus 38%, respectively; p=0.04).

A prospective randomized trial compared cyclosporine, modified (n=51) to tacrolimus (n=50) for primary immunosuppression.[108] One-hundred-one adult liver transplant patients were enrolled and followed for 5 years. At 1, 3, and 5 years, survival rates were 86%, 75%, and 72%, respectively with no significant difference between the 2 treatment arms. A total of thirty cases of acute rejection occurred with no significant difference between the 2 treatment groups. More cyclosporine patients reported serious adverse events than tacrolimus patients (48 versus 32 patients, respectively). More cyclosporine-treated patients (n=19) switched to the other calcineurin inhibitor than tacrolimus-treated patients (n=15). The switch was mainly due of lack of efficacy. There were no cases of chronic rejection in the tacrolimus arm. Four patients were switched from tacrolimus to cyclosporine, modified due to adverse effects. There was no difference between the 2 treatment groups in renal dysfunction, diabetes, hypertension, neurologic disorders, new-onset malignancies or infections, and there were no significant differences in survival or rejection among the intention-to-treat groups.

Cyclosporine, modified (n=250) was compared to tacrolimus (n=245) for safety and efficacy at 3 and 6 months and for patient status at 12 months in an open-label, multicenter study involving liver transplant recipients.[109] Participants also received steroids with or without azathioprine. At 12 months, 85% of cyclosporine, modified-treated patients and 86% of tacrolimus-treated patients survived with a functioning graft (p=NS). The cyclosporine, modified arm (6%) had significantly fewer hepatitis C-positive patients die or lose their graft by 12 months when compared to the tacrolimus arm (16%; p≤0.03). No difference was seen between the groups in recurrence of hepatitis C virus. At 12 months,

median serum creatinine concentration was 106 umol/L in both treatment groups. At 12 months, more tacrolimus-treated patients who were nondiabetic at baseline received antihyperglycemic therapy (13% versus 5%; p≤0.01), and more tacrolimus-treated patients who were diabetic at baseline required anti-diabetic treatment (70% versus 49%; p=0.02). Treatment for *de novo* or pre-existing hypertension or hyperlipidemia was similar in both groups.

A multicenter, randomized, open-label study compared tacrolimus (n=301) and cyclosporine, modified (n=305) in a total of 606 patients undergoing first orthotopic liver transplantation.[110] Patients in both treatment groups received combined treatment with a standard immunosuppressant regimen. The primary endpoint was the combined frequency of death, retransplantation, or treatment failure. Ninety-six percent of those randomized received the study treatment. An intention-to-treat analysis revealed the primary outcome was reached in 21% (n=62) of patients in the tacrolimus arm versus 32% (n=99) of patients in the cyclosporine, modified arm (relative risk [RR], 0.63; p=0.001). Death occurred in 50 (17%) tacrolimus patients versus 72 (24%) cyclosporine, modified patients; retransplantations were necessary in 11 (4%) versus 31 (10%); and treatment failure for immunological reasons occurred in 6 (2%) versus 12 (4%) patients, respectively. Sepsis and multi-organ failure were the main causes of death in both trial groups. No differences were seen between the 2 groups in the rate of renal dysfunction or the need for antihypertensive therapy; however, more tacrolimus-treated patients developed diabetes mellitus.

Renal Transplant

azathioprine (Imuran) versus cyclosporine

The long-term effects of azathioprine were compared to cyclosporine in live-donor kidney transplantation patients in a randomized study.[111] Adult primary renal transplant recipients aged between 18 and 60 years with 1 haplotype HLA mismatch who had been transplanted before 1988 were included. Four hundred seventy-five participants received a primary immunosuppressive protocol consisting of both steroid and azathioprine (n=300) or cyclosporine (n=175). Study endpoints included patient and graft survival rates, condition at last follow-up, rejection (acute and chronic), and graft function (serum creatinine and creatinine clearance). There was no significant difference between the groups in overall frequency of acute rejection episodes. The azathioprine-treated patients had graft survival rates of 69% versus 58% at 5 years, and 52% versus 36% at 10 years compared to cyclosporine treatment. However, at 20 years, graft survival rates had declined to 26% in the azathioprine arm and 24% in the cyclosporine arm. No significant differences were seen between the 2 groups regarding post-transplant malignancies, diabetes mellitus, hepatic impairment, or serious bacterial infections.

Recipients (n=112) of haploidentical live-related donor kidney transplants were randomly assigned prior to transplantation to receive azathioprine (n=54) or cyclosporine (n=58) combined with prednisone.[112] Patients were followed for 3 to 6 years (mean 50 ± 8 months). Thirteen azathioprine-treated patients (24%) and 6 cyclosporine-treated patients (10%) were switched to the alternate immunotherapy (p≥0.05). No significant differences were seen between the groups in patient survival, graft survival, or overall frequency of acute rejection during the follow-up period. However, the number of patients who had 2 or more rejection episodes was higher among the azathioprine-treated patients (p≤0.04). The mean serum creatinine concentrations were significantly higher in the cyclosporine arm at 1, 12, and 24 months after transplantation.

azathioprine (Imuran) versus mycophenolate mofetil (CellCept)

After cadaveric renal transplant, patients were randomized to receive tacrolimus in combination with either azathioprine (n=59) or mycophenolate mofetil 1 gram per day (n=59) or 2 grams per day (n=58) and followed for 1 year post-transplant.[113] Participants were evaluated for the incidence of biopsy-confirmed acute rejection, patient and graft survival, and adverse events. The tacrolimus dose and trough concentrations were similar between treatment groups at all time points. By 6 months post-transplant, the mean dose of mycophenolate mofetil decreased in the 2 gram group to 1.5 grams, primarily due to gastrointestinal-related adverse effects. The incidence of biopsy-confirmed acute rejection at 1 year was 32.2% in the azathioprine group, 32.2% in the mycophenolate mofetil 1 gram group, and 8.6% in the mycophenolate mofetil 2 grams group ($p \leq 0.01$). There was no difference among the 3 groups in the use of antilymphocyte antibodies for the treatment of rejection. The incidence of most adverse events was similar across treatment groups and comparable with previous reports. No differences were seen across the 3 treatment groups in the incidence of malignancies or opportunistic infections.

Antirejection activity and adverse events of mycophenolate mofetil were compared to azathioprine both with cyclosporine, modified and steroids (phase A) in recipients of cadaveric kidney transplants over 6 months in a multicenter, prospective, randomized, parallel-group trial.[114] Participants were then followed for an additional 15 months without steroids (phase B). The primary endpoint, occurrence of acute rejection episodes, was analyzed by intent-to-treat. One hundred sixty-eight patients per group entered phase A. Clinical rejections were seen in 56 patients (34%) assigned to mycophenolate mofetil and 58 patients (35%) assigned to azathioprine ($p=0.44$). Eighty-eight patients in the mycophenolate mofetil group and 89 in the azathioprine group entered phase B. Clinical rejections were seen in 14 patients (16%) taking mycophenolate mofetil and 11 patients (12%) taking azathioprine ($p=0.71$).

azathioprine (Imuran) versus sirolimus (Rapamune)

A prospective, multicenter, randomized, double-blind trial compared azathioprine to sirolimus added to cyclosporine and prednisone.[115] Recipients (n=719) of HLA-mismatched cadaveric or living-donor renal allografts who displayed initial graft function were randomly assigned to sirolimus 2 mg daily (n=284) or 5 mg daily (n=274) or azathioprine (n=161). At 6 and 12 months, the primary composite endpoint of efficacy failure, occurrence of biopsy-confirmed acute rejection episodes, graft loss, or death and various secondary endpoints that characterize these episodes were compared using an intention-to-treat analysis. The 2 sirolimus groups had a lower rate of efficacy failure at 6 months (2 mg: 18.7%, $p=0.002$; 5 mg: 16.8%, $p \leq 0.001$) compared to azathioprine (32.3%). In addition, the frequency of biopsy-confirmed acute rejection episodes was lower in the sirolimus groups (2 mg: 16.9%, $p=0.002$; 5 mg: 12%, $p \leq 0.001$) compared to azathioprine (29.8%). Survival was similar in all groups for grafts and patients at 12 months. Rates of infection and malignancies were similar among the groups.

cyclosporine versus sirolimus (Rapamune)

The efficacy and tolerability of a calcineurin inhibitor-free regimen was compared in a prospective, randomized trial.[116] One hundred forty-five renal transplant recipients were given either sirolimus (n=71) or cyclosporine (n=74) along with polyclonal antilymphocyte antibodies, mycophenolate mofetil, and steroids for 6 months. Estimated glomerular filtration rates, the primary endpoint, were not statistically different at 12 months between the 2 groups. In addition, patient and graft survival, delayed and slow graft function, incidence of biopsy-proven rejection, and rates of steroid withdrawal

were not statistically different between the groups at 12 months. Overall study drop-out rates were 28% with sirolimus and 14.9% with cyclosporine. In patients who remained on treatment according to protocol at 12 months, estimated glomerular filtration rates were significantly higher with sirolimus (69 ± 19 versus 60 ± 14 mL/min; p=0.01). Sirolimus-treated patients had more adverse events such as wound complications, mouth ulcers, diarrhea, hypokalemia, bronchopneumonia, and proteinuria > 0.5 g/24 hours compared to cyclosporine-treated patients (38.8% versus 5.6%; p≤0.001). Additionally, sirolimus-treated patients experienced significantly fewer cytomegalovirus (CMV) infections compared to cyclosporine-treated patients (6% versus 23%; p≤0.01).

A 6-month, randomized, open-label, multicenter prospective study was conducted to evaluate the effects of sirolimus (n=33) versus cyclosporine (n=36) each in combination with antithymocyte globulin induction, mycophenolate mofetil, and steroids in recipients of kidney transplant.[117] More sirolimus-treated patients withdrew because of delayed graft function and surgical complications (16 versus 6; p≤0.01). In addition, delayed graft function tended to be more frequent among sirolimus recipients (45.4% versus 30.6%; p=0.22), but graft survival was similar (87.5% versus 97%; p=0.19). At 6 months, there were no significant differences in biopsy-proven acute rejection or calculated creatinine clearance.

A randomized, prospective trial of 61 adult primary kidney transplant recipients compared sirolimus with cyclosporine.[118] Each patient received induction therapy with 20 mg basiliximab (Simulect®) on days 0 and 4, and maintenance therapy with mycophenolate mofetil 1 gram twice daily and steroids. Sirolimus doses were titrated to maintain 24-hour trough concentrations of 10 to 12 ng/mL for 6 months and 5 to 10 ng/mL thereafter. Cyclosporine therapy was titrated to maintain 12-hour trough concentrations of 200 to 250 ng/mL. Participants were followed for a mean duration of 18.1 months (range, 12 to 26 months). No differences were seen between the treatment groups in percentages of 1 year patient survival, graft survival, or biopsy-confirmed acute rejection rates. At 6 and 12 months, respectively, sirolimus-treated patients showed significantly better mean serum creatinine concentrations (1.29 and 1.32 mg/dL, respectively) and calculated creatinine clearances (77.8 and 81.1 mL/min, respectively) than cyclosporine-treated patients (1.74 and 1.78 mg/dL, and 64.1 and 61.1 mL/min, respectively, p=0.008 and p=0.004). Significantly higher 1-year trough concentrations of mycophenolic acid were seen in the sirolimus-treated recipients (4.16 ng/mL versus 1.93 ng/mL, p=0.001).

Sirolimus (n=41) was compared to cyclosporine (n=42) in first cadaveric renal allograft recipients in 11 European centers.[119] Each agent was titrated to appropriate blood concentrations and combined with corticosteroids and azathioprine. Results showed similar graft survival (98% sirolimus versus 90% cyclosporine), patient survival (100% versus 98%), and incidence of biopsy-confirmed acute rejection (41% versus 38%) at 12 months. At 3 and 4 months, serum creatinine was significantly lower with sirolimus (p≤0.05), and serum uric acid and magnesium were normal. Sirolimus-treated patients experienced laboratory abnormalities including hypertriglyceridemia (51% versus 12%), hypercholesterolemia (44% versus 14%), thrombocytopenia (37% versus 0%), leukopenia (39% versus 14%), and, of lesser importance, increased liver enzymes and hypokalemia more often. When the sirolimus target serum trough concentrations were lowered from 30 to 15 ng/mL two months after transplantation, these abnormalities improved. The occurrence of CMV was comparable (14% versus 12%); however, pneumonia incidence (17% versus 2%; p=0.03) was higher with sirolimus. The difference in incidences of herpes simplex was in favor of the sirolimus group (24% versus 10%; p=0.08) but was not statistically significant. The sirolimus-treated patients experienced no gingival hyperplasia,

rare tremor, less frequent hypertension (17% versus 33%), and no malignancies. Two malignancies were observed with cyclosporine.

In a study, patients (n=448) were randomly assigned before transplant to receive sirolimus and tacrolimus (SRL+TAC) or sirolimus and cyclosporine (SRL+CsA), each with corticosteroids.[120] Both treatments demonstrated equivalent efficacy of the composite endpoint at 12 months with efficacy failure rates of 21.9% versus 23.2% (SRL+TAC versus SRL+CsA, respectively; p=0.737). Biopsy-confirmed acute rejection rate (13.8% versus 17.4%) and graft survival rate (89.7% versus 90.2%) were similar. In evaluable patients, renal function was not superior in SRL+TAC versus SRL+CsA (54.5 versus 52.6 mL/min, p=0.466). At 12 months, there were no significant differences in rates of death, discontinuation because of adverse events, hypercholesterolemia, hyperlipemia, or proteinuria. Diarrhea and herpes simplex infections occurred significantly more often in SRL+TAC patients. Hypertension, cardiomegaly, increased creatinine, overdose (primarily calcineurin inhibitor toxicity), acne, urinary tract disorders, lymphocele, and ovarian cysts occurred significantly more often in SRL+CsA patients.

A prospective, open-label, multicenter randomized study evaluated the conversion of 192 patients from a cyclosporine-based regimen to a sirolimus-based regimen 3 months after transplantation.[121] All patients were also given mycophenolate mofetil and oral steroids, which were planned to be discontinued after 8 months. The primary endpoint, creatinine clearance week 52, was significantly better in the sirolimus group (68.9 versus 64.4 mL/min, p=0.017). However, patient and graft survival were not statistically different. The incidence of acute rejection episodes, mainly occurring after withdrawal of steroids, was not statistically higher in the sirolimus group (17% versus 8%, p=0.071). Significantly more patients in the sirolimus group reported aphthous, diarrhea, acne, and high triglyceride concentrations.

A multicenter, prospective trial included 193 kidney recipients randomized at week 12 to switch from cyclosporine to sirolimus or to continue cyclosporine.[122] All patients received mycophenolate mofetil. Quantified assessment of interstitial fibrosis by a program of color segmentation was performed at 1 year in 121 patients. At 1 year, renal function was significantly improved in the conversion group. Biopsy results, however, showed no between-group difference in percentage of interstitial fibrosis.

An open-label, parallel-group, comparative trial randomized 487 patients 2:1 to sirolimus or cyclosporine.[123] All patients received basiliximab induction as well as maintenance mycophenolate mofetil and corticosteroids along with either sirolimus or cyclosporine. Within 6 months of the start of the trial, an imbalance in the incidence of acute rejection was noted. The data monitoring committee noted the sirolimus trough levels were below the target range in 39% of patients 2 weeks after transplantation. A protocol amendment increased the loading dose of sirolimus. However, the imbalance in acute rejection rates continued despite the protocol amendment and at one year the study was terminated due to the increased BCAR rate in the sirolimus group.

cyclosporine versus tacrolimus (Prograf)

Two hundred patients were randomized in a 2:1 fashion to receive tacrolimus (n=134) or cyclosporine (n=66) along with thymoglobulin induction, an antimetabolite, and prednisone.[124] At 1 year, efficacy was similar between the groups. The rate of acute rejection was 4% in the tacrolimus group and 6% in the cyclosporine group. The rate of patient survival was 99% in the tacrolimus group and 100% in the cyclosporine group, and the rate of graft survival was 95% in the tacrolimus group and 100% in the cyclosporine group. Serum creatinine concentrations were lower in the tacrolimus group compared

with the cyclosporine group (1.3 ± 0.3 versus 1.6 ± 0.7 mg/dL, p=0.03). The incidences of CMV infection, anti-hypertensive requirement, and post-transplant diabetes mellitus were similar; however, 2 patients in the tacrolimus arm developed malignancy.

A multicenter, randomized trial comparing the 12-month efficacy and safety of tacrolimus-based to cyclosporine-based immunosuppressive regimens in the prevention of renal allograft rejection enrolled 448 renal transplant recipients assigned to receive triple-drug therapy consisting of tacrolimus (n=303) or cyclosporine (n=145), each in combination with azathioprine and low-dose corticosteroids.[125] Results showed that tacrolimus therapy was associated with a significant reduction in the frequency of both acute rejection (tacrolimus 25.9% versus cyclosporine 45.7%; p≤0.001) and corticosteroid-resistant rejection (11.3% versus 21.6%; p=0.001) at 12 months. No significant differences were seen between the groups in 1-year patient survival (tacrolimus, 93% versus cyclosporine, 96.5%; p=0.14) and graft survival rates (82.5% versus 86.2%; p=0.38). The safety profiles of the tacrolimus- and cyclosporine-based regimens were similar. The tacrolimus treatment group reported higher incidences of elevated serum creatinine, tremor, diarrhea, hyperglycemia, diabetes mellitus, and angina pectoris; however, the cyclosporine treatment group reported higher incidences of acne, arrhythmia, gingival hyperplasia, and hirsutism.

In a randomized, open-label study, 412 patients receiving cadaveric kidney transplants were randomized to tacrolimus (n=205) or cyclosporine (n=207) and followed for 1 year.[126] Assessments were done for patient and graft survival and the incidence of acute rejection. One-year patient survival rates were 95.6% for tacrolimus and 96.6% for cyclosporine (p=0.576), and 1-year graft survival rates were 91.2% for tacrolimus and 87.9% for cyclosporine (p=0.289). The incidence of biopsy-confirmed acute rejection was significantly reduced in the tacrolimus group compared with the cyclosporine group (30.7% versus 46.4%; p=0.001). Both treatment groups reported impaired renal function, gastrointestinal disorders, and neurological complications; however, tremor and paresthesia were more frequently reported in the tacrolimus group. The incidence of post- transplant diabetes mellitus was 19.9% in the tacrolimus group and 4% in the cyclosporine group (p≤0.001).

Cyclosporine-treated patients who had an elevated serum creatinine (SCr) at least 3 months post-renal transplantation (n=186) were randomized in a 2:1 fashion to switch to tacrolimus or continue cyclosporine.[127] On baseline biopsy, 90% of patients had chronic allograft nephropathy, and baseline median SCr was 2.5 mg/dL in both treatment groups. For patients with graft function at month 24, SCr had decreased to 2.3 mg/dL in the tacrolimus-treated patients and increased to 2.6 mg/dL in the cyclosporine-treated patients (p=0.01). During the follow-up, acute rejection occurred in 4.8% of tacrolimus-treated patients and 5% of cyclosporine-treated patients. The 2 groups were comparable for 2-year allograft survival (tacrolimus 69%, cyclosporine 67%; p=0.7). Tacrolimus-treated patients experienced lower cholesterol and low-density lipoprotein concentrations along with fewer new-onset infections. In addition, cardiac conditions developed in fewer tacrolimus-treated patients compared to cyclosporine-treated patients (5.6% versus 24.3%; p=0.004). The 2 groups did not differ in glucose concentrations, incidences of new-onset diabetes, or new-onset hyperglycemia.

cyclosporine, modified (Gengraf/Neoral) versus tacrolimus (Prograf)

Cyclosporine modified was compared to tacrolimus in a multicenter, randomized, 6-month open-label study involving 560 patients.[128] Patients were given azathioprine and corticosteroids in addition to either tacrolimus (n=287) at an initial oral daily dose of 0.3 mg/kg or cyclosporine, modified (n=273) at an initial oral daily dose of 8 to 10 mg/kg. The proportion of patients with biopsy-proven acute

rejection and the time to the event was the primary endpoint. Tacrolimus-treated patients had a lower rate of biopsy-confirmed acute rejection when compared to cyclosporine, modified (56 patients [19.6%] versus 101 [37.3%]; p≤0.0001). Tacrolimus-treated patients also had a lower incidence of biopsy-confirmed corticosteroid-resistant rejection when compared to cyclosporine, modified (27 [9.4%] versus 57 [21%]; p≤0.0001). Crossover between therapies secondary to biopsy-proven rejection was necessary in 1 (0.3%) tacrolimus-treated patient and 27 (10%) cyclosporine, modified-treated patients (p≤0.0001). The 2 treatment groups had similar rates of patient and graft survival and similar renal function. In addition, the overall rates of adverse events were similar in the 2 groups. However, hypertension and hypercholesterolemia were more common in the cyclosporine, modified-treated patients, and tremor and hypomagnesaemia were more frequent in the tacrolimus-treated patients.

A prospective, randomized trial compared the effect of cyclosporine, modified to tacrolimus on the development of renal allograft fibrosis, defined as chronic allograft nephropathy (CAN).[129] One hundred two patients undergoing renal transplantation were given either cyclosporine, modified (15 mg/kg per day adjusted to whole-blood trough concentrations of 200 to 300 ng/mL) or tacrolimus (0.2 mg/kg per day adjusted to whole-blood trough concentrations of 8 to 15 ng/mL) in conjunction with steroids and azathioprine. The 2 drugs were compared using concentrations of interstitial fibrosis in relation to observed efficacy and toxicity profiles. No difference was seen between the groups in demographic characteristics, incidence of acute rejection (cyclosporine, modified 36% versus tacrolimus 35%), or steroid-resistant rejection (both 10%). The cyclosporine, modified-treated patients had a significant increase in allograft interstitial fibrosis. There was a higher incidence of insulin resistance in the tacrolimus group; however, this did not reach statistical significance. Cyclosporine was associated with a significant increase in total cholesterol and low-density lipoprotein concentrations, which persisted throughout the study period (p=0.03 and p=0.021, respectively).

everolimus (Zortress) and mycophenolate mofetil (CellCept)

In a randomized, multicenter, multinational, 12-month, double-blind, double-dummy, open-label, phase 3 trial in *de novo* renal allograft recipients (n=588), everolimus 1.5 mg or 3 mg daily was compared with mycophenolate mofetil 2 grams daily.[130] Patients also received cyclosporine and corticosteroids as part of a triple immunosuppressive regimen. At 12 months, there were no statistically significant differences between everolimus 1.5 mg, everolimus 3 mg, and mycophenolate mofetil in the incidence of biopsy-proven acute rejection (23.2%, 19.7%, and 24%, respectively), graft loss (4.6%, 10.6%, and 9.2%), or death (5.2%, 4%, and 2.6%). Everolimus 1.5 mg and mycophenolate mofetil were equally well tolerated. Both were better tolerated than everolimus 3 mg. The incidence of CMV infection was significantly lower in patients receiving everolimus 1.5 mg or 3 mg than in those receiving mycophenolate mofetil (5.2%, 7.6%, and 19.4%, respectively; p=0.001).

A 36-month, randomized, parallel-group study compared everolimus 1.5 mg and 3 mg daily with mycophenolate mofetil 2 grams daily in *de novo* renal-transplant recipients (n=583).[131] Patients also received full-dose cyclosporine and corticosteroids after randomization. For at least their first year, patients received study medication according to a double-blinded, double-dummy design before concerns over nephrotoxicity led to an amended open-label design with reduced cyclosporine troughs. Incidences of primary efficacy failure at 36 months (biopsy-proven acute rejection, graft loss, death, or loss to follow-up) were 33.7%, 34%, and 31.1% for everolimus 1.5 mg, everolimus 3 mg/day, and mycophenolate mofetil, respectively (p=0.810). Antibody-treated acute rejection at 36 months was significantly lower with everolimus 1.5 mg than mycophenolate mofetil (9.8% versus 18.4%; p=0.014).

Discontinuation for adverse events, including death and graft loss, was more frequent with everolimus compared to the mycophenolate mofetil arm.

everolimus (Zortress) and mycophenolate sodium (Myfortic)

In a 24-month, open-label study, 833 *de novo* renal transplant recipients were randomized to everolimus 1.5 mg or 3 mg daily with reduced-exposure cyclosporine or mycophenolate 1.44 grams daily plus standard-exposure cyclosporine.[132] Patients received basiliximab (Simulect) with or without corticosteroids. The primary endpoint was composite efficacy failure (treated biopsy-proven acute rejection, graft loss, death, or loss to follow-up) and the main safety endpoint was renal function at month 12 (last observation carried forward). Month 12 efficacy failure rates were non-inferior in the everolimus 1.5 mg and 3 mg versus mycophenolate groups (25.3%, 21.9%, and 24.2%, respectively). Mean eGFR at month 12 was non-inferior in the everolimus groups versus the mycophenolate group. The overall incidence of adverse events was comparable between groups.

mycophenolate sodium (Myfortic) and mycophenolate mofetil (CellCept)

Mycophenolate sodium (720 mg twice daily) was compared to mycophenolate mofetil (1,000 mg twice daily) combined with cyclosporine, modified and corticosteroids in 423 *de novo* kidney transplant patients in a 12-month, double-blind study.[133] At 6 months, mycophenolate sodium proved to be equivalent to mycophenolate mofetil in efficacy failure, defined by biopsy-proven acute rejection, graft loss, death, or loss to follow up (25.8% versus 26.2% [95% CI, -8.7 to 8]). At 12 months, the incidence of efficacy failure was 26.3% for mycophenolate sodium and 28.1% for mycophenolate mofetil, and the incidence of biopsy-proven acute rejection was 22.5% for mycophenolate sodium and 24.3% for mycophenolate mofetil. The rate of severe acute rejection was 2.1% with mycophenolate sodium and 9.8% with mycophenolate mofetil among those with biopsy-proven acute rejection (p=NS). The incidence of adverse events was similar between the groups. Within 12 months, 15% of mycophenolate sodium and 19.5% of mycophenolate mofetil patients required a dose change due to GI adverse events (p=NS).

In a single-center, open-label, randomized trial, mycophenolate mofetil (group A, n=75) was compared to enteric-coated mycophenolate sodium (group B, n=75) in primary renal transplant recipients receiving combined thymoglobulin/daclizumab induction along with reduced tacrolimus dosing and elimination of corticosteroids 1 week postoperatively.[134] The primary endpoint was the incidence rate of acute rejection during the first 12 months post-transplant. Secondary aims were to compare graft and patient survival, renal function, drug dosing and monitoring, gastrointestinal adverse effects, and other adverse events at 12 months of follow-up. Patient/graft survival in groups A and B were 100%/96% versus 99%/96%, respectively (p=NS). At 12 months, 3% versus 9% in group A and group B, respectively, experienced biopsy-proven acute rejection (p=NS). Incidence of new onset diabetes mellitus, infections requiring hospitalization, and GI adverse effects appeared equivalent.

mycophenolate mofetil (CellCept) versus sirolimus (Rapamune)

The impact on graft survival and long-term graft function in renal transplant recipients using maintenance therapy consisting of either mycophenolate mofetil or sirolimus, each without prednisone, was compared.[135] Induction therapy was given on days 0, 1 and 2 post-transplant. Patients were then prospectively randomized to 2 maintenance immunosuppressive regimens with tacrolimus plus mycophenolate mofetil (n=45) or tacrolimus plus sirolimus (n=37). During the 3-year follow-up, there was 1 kidney loss in the mycophenolate mofetil group versus 6 losses in the sirolimus group

(p=0.04). Glomerular filtration rates at different time-points post-transplant were better, and the slope of glomerular filtration rate decline per month was flatter in the mycophenolate mofetil arm compared to the sirolimus arm.

A 1-year, randomized, multicenter clinical trial was conducted comparing the combination of sirolimus (n=185) or mycophenolate mofetil (n=176) with tacrolimus and corticosteroids in kidney transplant patients.[136] The primary endpoint of the study was the incidence of biopsy-confirmed acute rejection at 6 months. Patient and graft survival, renal function, study drug dosing and discontinuations were evaluated at 1 year, and results showed no differences in patient or graft survival. However, patients without delayed graft function receiving mycophenolate mofetil had significantly better graft survival (99% versus 93%; p=0.01), and those receiving a transplant from a live donor had a trend towards better graft survival with mycophenolate mofetil (98% versus 91%; p=0.07). The sirolimus-treated group had a higher incidence of study drug discontinuations (26.5% versus 14.8%; p=0.006). The mycophenolate mofetil-treated patients had better mean serum creatinine concentrations (1.3 mg/dL versus 1.5 mg/dL; p=0.03) and a trend towards higher calculated creatinine clearance (58.4 mL/min versus 54.3 mL/min; p=0.06). More sirolimus-treated patients experienced serum creatinine concentrations greater than 2 mg/dL (20.4% versus 11%; p=0.02).

One hundred kidney transplant recipients receiving tacrolimus-based immunosuppressive regimens were randomized into equal groups and given mycophenolate mofetil 2 grams per day or sirolimus at a loading dose of 150 mg followed by 5 mg daily until day seven and 2 mg daily thereafter.[137] No differences were observed in incidences of the composite primary endpoint, biopsy-confirmed acute rejection, graft loss, and death. In addition, no differences were seen between the groups in biopsy-confirmed acute rejection or 1-year patient, graft, or death-censored graft survival. However, patients treated with sirolimus had a higher mean creatinine (1.6 ± 0.5 mg/dL versus 1.4 ± 0.3 mg/dL; p=0.007), incidence of proteinuria (52% versus 10.7%; p=0.041), mean urinary protein concentrations (0.3 ± 0.5 g/L versus 0.1 ± 0.2 g/L; p=0.012), mean cholesterol (217 mg/dL versus 190 mg/dL; p=0.03), and percentage of premature drop outs (26% versus 8%; p=0.031) when compared to the mycophenolate mofetil-treated patients.

In addition to tacrolimus, 325 participants were given sirolimus 2 mg daily, 325 participants were given sirolimus 0.5 mg daily, and 327 participants were given mycophenolate mofetil 1 gram daily.[138] Initially, the tacrolimus dose was 0.2 mg/kg daily, and the sirolimus loading dose was 6 or 1.5 mg followed by a daily dose of 2 or 0.5 mg. All groups received identical steroid doses. The sirolimus 2 mg group had a lower incidence (15.7%) of biopsy-proven acute rejection compared with the sirolimus 0.5 mg (25.2%; p=0.003) group and the mycophenolate mofetil (22.3%; p=0.036) group. Six-month graft survival was 91% for the sirolimus 2 mg arm, 92.6% for the sirolimus 0.5 mg arm, and 92.4% for the mycophenolate mofetil arm. The respective values for patient survival were 98.1%, 97.8%, and 97.9%. Study drop-out rates due to adverse events were as follows: 34 patients (10.5%) in the sirolimus 2 mg group, 19 patients (5.8%) in the sirolimus 0.5 mg group, and 16 patients (4.9%) in the mycophenolate mofetil group. More patients in the sirolimus 2 mg group experienced hyperlipidemia compared with the sirolimus 0.5 mg and the mycophenolate mofetil group (24%, 19.4%, and 11%, respectively).

sirolimus (Rapamune) versus tacrolimus (Prograf)

A prospective, randomized trial compared the safety and efficacy of sirolimus (target concentration 12 to 18 ng/dL in the first month) to tacrolimus (target concentration 12 to 15 ng/mL in the first month) each combined with mycophenolate mofetil 750 mg twice daily, prednisone tapered to 10 mg per day

by 3 months and immunosuppressant induction with thymoglobulin.[139] Preliminary results at 4 months in 85 patients showed acute rejection rate of 7.5% in the tacrolimus group compared to 6.7% in the sirolimus group. Eight sirolimus patients withdrew from the study, most commonly due to wound complications. At 1 month, renal function appeared to be better in the sirolimus group; however, this had not reached statistical significance.

tacrolimus extended-release capsules (Astagraf XL) versus tacrolimus (Prograf)

A randomized, open-label, multicenter, trial compared tacrolimus ER capsules (Astagraf) to tacrolimus immediate-release over 12 months in patients with a kidney transplant.[140] All patients received basiliximab induction and concomitant treatment with MMF and corticosteroids. Patients 17 to 77 years of age were randomized to receive tacrolimus ER capsules (Astagraf XL) (n=214) 0.15 mg/kg/day or tacrolimus immediate-release (n=212) 0.1 mg/kg/day. The primary efficacy outcome was the percentage of patients who developed biopsy-proven acute rejection (BPAR), graft failure, death, and/or were lost to follow-up at 12 months. In the tacrolimus ER capsule (Astagraf XL) group 30 (14%) patients experienced the combined outcome compared to 32 (15.2%) in the tacrolimus immediate-release group with treatment difference of -1.1% (95% CI, -7.8 to 5.6). Premature discontinuation from treatment at the end of 1 year occurred in 14% of tacrolimus ER capsules (Astagraf XL) patients and 16% of tacrolimus immediate-release patients, primarily due to adverse reactions.

A randomized, double-blind, multicenter, trial of identical trial design with the exception of no basiliximab induction compared tacrolimus ER capsules (Astagraf XL) to tacrolimus immediate-release over 12 months in patients receiving a kidney transplant. All patients received concomitant treatment with MMF and corticosteroids without antibody induction.[141] Patients 18 to 65 years of age were randomized to receive tacrolimus ER capsules (Astagraf XL) (n=331) or tacrolimus immediate-release (n=336) at a pre-operative dose of 0.1 mg/kg/day and a post-operative dose of 0.2 mg/kg/day. After post-operative day 1, the doses were altered to achieve comparable mean tacrolimus trough concentrations between tacrolimus ER capsules (Astagraf XL) and tacrolimus immediate-release. Higher total mean daily doses of tacrolimus ER capsules (Astagraf XL) were required than tacrolimus immediate-release dose, on average by 25%. The primary efficacy outcome was the percentage of patients who developed biopsy-proven acute rejection (BPAR), graft failure, death, and/or lost to follow-up at 12 months. In the tacrolimus ER capsules (Astagraf XL) group 93 (28%) patients experienced the outcome compared to 78 (23%) in the tacrolimus immediate-release group with treatment difference of 4.9% (95% CI, -1.7 to 11.5). Premature discontinuation from treatment at the end of 1 year occurred in 24% of tacrolimus ER capsules (Astagraf XL) patients and 19% of tacrolimus immediate-release patients, primarily due to adverse reactions.

A phase 3 randomized, open-label, comparative, noninferiority study examined 638 patients *de novo* kidney transplants.[142] Patients were randomized to 1 of 3 treatment arms: tacrolimus, ER capsules once daily, tacrolimus twice daily, or cyclosporine twice daily. All patients received basiliximab induction, mycophenolate mofetil and corticosteroids. Patients were followed for 4 years. Four-year Kaplan-Meier estimates of patient survival were 93.2%, 91.2%, and 91.7%, respectively for tacrolimus ER capsules, tacrolimus immediate-release and cyclosporine arms. Graft survival was 84.7%, 82.7% and 83.9% in these same groups. Adjusted mean differences in renal function, as measured by the Cockcroft-Gault formula, over the 4-year period were not statistically different between tacrolimus ER and tacrolimus immediate-release, but there was a statistically significant difference, favoring tacrolimus ER when compared to cyclosporine (p=0.0118). Evidence of treatment–emergent glucose intolerance in the continuation phase was more common in the tacrolimus ER and tacrolimus

immediate-release groups compared to the cyclosporine group. Rates of HbA1c ≥ 6.5% over time were statistically significantly lower in the cyclosporine group compared to the tacrolimus-based groups (log rank test: tacrolimus versus cyclosporine, p=0.01, tacrolimus ER versus cyclosporine, p=0.0006).

tacrolimus extended-release tablets (Envarsus XR) versus tacrolimus (Prograf)

A randomized, open-label trial was conducted in 324 patients who were between 3 months and 5 years post-kidney transplant and who were receiving a stable, therapeutic dose of tacrolimus immediate-release (IR) (Prograf).[143] Patients were randomized to once daily tacrolimus ER tablets or maintained on twice daily IR tacrolimus. Concomitant mycophenolate, azathioprine, and/or corticosteroids were allowed. The efficacy failure rates (patients who developed biopsy proven acute rejection, graft failure, death, and/or lost to follow up) at 12 months did not differ between the 2 groups (0%; 95% CI, -4.2 to 4.2), nor did the estimated glomerular filtration rates (eGFR) at 12 months.

Psoriasis

cyclosporine (Sandimmune) and cyclosporine, modified (Neoral)

Patients with severe, chronic, plaque-type psoriasis were randomized on a 1:1 basis to 24 weeks of cyclosporine, modified (n=152) or cyclosporine (n=157) at a starting dose of 2.5 mg/kg per day.[144] Dose increases were allowed after 4 weeks to maintain efficacy, and for patients who achieved remission, dose decreases were allowed after 16 weeks at 4-week intervals. The maximum permitted dose for each formulation was 5 mg/kg per day. Since remission rates were higher for cyclosporine, modified during the first 8 weeks of treatment, it was concluded that cyclosporine, modified produced a more rapid response than cyclosporine. The number of dose reductions for safety was similar in both groups; however, there were more dose increases to maintain efficacy in the cyclosporine group than the cyclosporine, modified group. There were no differences between groups in the frequency or type of adverse events seen. The mean dose required to control disease was 10% lower with fewer dose adjustments needed in the cyclosporine, modified group than in the cyclosporine group.

Rheumatoid Arthritis

azathioprine (Imuran) versus methotrexate

Azathioprine was compared to methotrexate in a randomized, double-blind fashion for the treatment of patients with RA in whom parenteral gold and/or D-penicillamine treatment had been ineffective.[145] Participants were given azathioprine (n=33) 100 mg daily or methotrexate (n=31) 7.5 mg weekly for 8 weeks. After 8 weeks, the dosage was increased if needed based on clinical improvement for a total intervention time of 48 weeks. Treatments were compared at 24 weeks with baseline values and showed improvements in 12 of 13 disease variables in the methotrexate group and in 6 of 13 in the azathioprine group. A significant overall clinical improvement, measured by disease activity score, was found in 7 of 20 patients treated with azathioprine and 18 of 30 treated with methotrexate after 24 weeks of treatment. At 48 weeks, a significant overall clinical improvement was seen in 6 of 12 azathioprine-treated patients and 19 of 25 methotrexate-treated patients. The number of dropouts due to adverse events was significantly higher in the azathioprine group. After 48 weeks, 12 azathioprine-treated patients (36%) and 25 methotrexate-treated patients (81%) were still using the initial therapy.

Sixty-four patients with active RA who either had not responded to or who had intolerable adverse effects with parenteral gold and D-penicillamine where given either azathioprine 100 mg daily or

methotrexate 7.5 mg weekly in a double-blind, randomized 48-week trial.[146] After 8 weeks of therapy, the dose was increased to either azathioprine 150 mg daily or methotrexate 15 mg weekly. Clinical and laboratory assessments were done every 4 weeks for the first 24 weeks then every 8 weeks for the remainder of the 48 week trial by the same physician. Initial radiologic scores were comparable in both groups and correlated with disease duration. An intention-to-treat analysis after 24 weeks showed significantly fewer new erosions in the methotrexate group compared to the azathioprine group (2 [95% CI, 0.2 to 3.9] and 48 (3.5 [95% CI, 1.3 to 5.8]). After 24 weeks, the change in joint score was also significantly less pronounced in the methotrexate group than in the azathioprine group (difference, 2.8 [95% CI, 0.2 to 5.2]). After 48 weeks, the change in joint score was significantly less pronounced in the methotrexate-treated patients compared to the azathioprine-treated patients as well (difference 3.9 [95% CI, 0.3 to 7.4]). Ten percent of the azathioprine group had reached radiologic stabilization after 48 weeks compared to 29% of the methotrexate group.

cyclosporine versus azathioprine (Imuran)

Patients with severe RA were randomized to receive cyclosporine (n=25) or azathioprine (n=27) for 6 months.[147] The initial mean dose of cyclosporine was 4.2 mg/kg and the initial mean dose of azathioprine was 1.7 mg/kg. At 6 months, the mean dose of cyclosporine was 3.4 mg/kg and the mean dose of azathioprine was 1.9 mg/kg. Both treatment groups exhibited statistically significant improvement in standard outcome parameters compared to baseline values. However, there were no statistically significant differences in these same parameters between the 2 study groups. Although no one withdrew due to impaired renal function, there was a mean increase in serum creatinine associated with cyclosporine.

A prospective, randomized, double-blind, multicenter study compared cyclosporine (starting dose 5 mg/kg) to azathioprine (1.5 to 2 mg/kg) in 117 patients with RA.[148] Ninety-two patients completed the 6-month study. Results showed mean improvement rate using the Ritchie-Index of 8.2, morning stiffness of 41.6 minutes, grip strength of 10.9 mmHg, and swollen joint count of 28.9% in cyclosporine-treated patients compared to 7.7, 28.4 minutes, 15.2 mmHg, and 27.9%, respectively in the azathioprine-treated patients. Treatment was discontinued early in 12 patients in each group. No differences in the efficacy or safety outcomes measured reached statistical significance.

cyclosporine (Sandimmune) and cyclosporine, modified (Neoral)

A 52-week, double-blind, multicenter, parallel-group study involving 51 patients with RA receiving stable conventional cyclosporine maintenance treatment was conducted.[149] Participants were randomized to continue conventional therapy (n=27) or to convert to cyclosporine, modified (n=24). Cyclosporine trough blood concentrations were measured before conversion and at specified intervals after conversion. Cyclosporine area under the curve at steady-state was assessed at 1 week before and 6 weeks after randomization in 15 patients in each treatment arm. Cyclosporine doses were titrated as needed based on disease activity and clinical evaluation in both groups. The initial mean daily doses of cyclosporine were 3.5 mg/kg per day compared to 3.3 mg/kg per day in the cyclosporine, modified group and did not change significantly during the study period. The mean bioavailability was 23% higher in the cyclosporine group compared to the cyclosporine, modified group; however, cyclosporine, modified had a more reproducible pharmacokinetic profile. Results were similar for overall incidence and nature of adverse events and changes in vital signs and laboratory variables. There was no significant difference in efficacy between the groups, and no loss of efficacy or intolerability was seen when recipients were switched from cyclosporine to cyclosporine, modified.

Lymphangioleiomyomatosis (LAM)

sirolimus (Rapamune) versus placebo

A total of 89 patients with LAM who had moderate lung impairment were randomized in a double blind trial comparing sirolimus with placebo.[150] Patients were treated for 12 months followed by a 12 month observation period. The primary end point was the difference between the groups in the rate of change (slope) for forced expiratory volume in 1 second (FEV_1). During the 12-month treatment period, the FEV_1 slope was 12 ± 2 mL per month in the placebo group and 1 ± 2 mL per month in the sirolimus group ($p<0.001$). The absolute mean change in FEV_1 during the treatment period between the 2 groups was 153 mL or approximately 11% of the mean FEV_1 at enrollment. The sirolimus group had improvement from baseline to 12 months in forced vital capacity, functional residual capacity, serum vascular endothelial growth factor D (VEGF-D), functional performance and quality of life compared to the placebo group. There was no significant difference between the 2 groups in 6-minute walk distance or diffusing capacity of the lung for carbon monoxide. After discontinuation of sirolimus, the decline in lung function for the previously treated sirolimus group paralleled the placebo group decline. Adverse events were more common in the sirolimus group but the frequency of serious adverse events did not differ significantly between the 2 groups.

META-ANALYSES

A meta-analysis of 20 retrospective studies involving 4,580 patients assessed risk factors for the development of new onset diabetes mellitus (NODM) after liver transplantation. [151] Regarding drug therapy, the results revealed the use of tacrolimus was found to be a significant risk factor (OR, 1.34; 95% CI, 1.03 to 1.76; p=0.03). Other non-drug related factors found to be significantly associated with the development of NODM included hepatitis C virus infection, a family history of diabetes, male gender, impaired fasting glucose, and a high body mass index.

SUMMARY

Currently marketed oral immunosuppressants are primarily utilized in the setting of organ transplantation. Azathioprine and cyclosporine are approved for the treatment of rheumatoid arthritis and cyclosporine is approved for the treatment of plaque psoriasis; however, these agents are far down the line of recommended treatment options for these disorders. Sirolimus (Rapamune) is the only treatment for rare a progressive disease, lymphangioleiomyomatosis (LAM), to help stabilize lung function.

The goal of immunosuppressant therapy in a transplant patient is to prolong graft survival, minimize episodes of rejection and improve overall survival while minimizing adverse effects of the drug. While guidelines for kidney transplantation suggest tacrolimus as the first-line calcineurin inhibitor and mycophenolate as the first-line antiproliferative agent, the best immunosuppressant regimen for a transplant patient should be one individualized based on adverse effect profile, tolerability, type of organ transplanted, and rejection patterns.

The use of corticosteroids has historically been associated with immunosuppression. While corticosteroids are still widely utilized during induction phases of immunosuppression and to treat acute or chronic graft rejection, the goal is to minimize their utilization during long-term maintenance therapy due to the adverse effects seen with long term therapy.

Cyclosporine (Gengraf, Neoral, Sandimmune) and tacrolimus (Prograf, Astagraf XL, Envarsus XR) are effective calcineurin inhibitors with a well established role in the prophylaxis of organ rejection. While treatment with any formulation of cyclosporine has been found to reduce the incidence of graft rejection, the Gengraf and Neoral formulations are preferred due to their more reliable pharmacokinetic profiles, which result in greater ease of monitoring. Blood concentration of calcineurin inhibitors are routinely monitored in order to keep patients in a therapeutic range that maximizes antirejection properties while minimizing adverse effect potential. Cyclosporine has been used successfully to prevent rejection in heart, liver and renal transplantation, but tacrolimus is often used instead, especially in renal transplantation, due to the established nephrotoxic effects of cyclosporine. Two extended-release tacrolimus preparations (Astagraf XL, Envarsus XR) offer once-daily dosage options in renal transplantation. Cyclosporine is still, however, a preferred agent in heart and heart/lung transplants.

In the setting of renal transplantation, current standard induction protocols followed by a maintenance regimen of a calcineurin inhibitor plus an antiproliferative agent and corticosteroids have resulted in 1 year graft survival rate approaching 90% and acute rejection rates of 20% or less. However, the calcineurin inhibitors, cyclosporine and tacrolimus, are associated with nephrotoxicity as well as other long-term toxicities. Recent protocols are exploring the outcomes associated with calcineurin inhibitor-free or calcineurin inhibitor-reduced exposure to determine both short and long term efficacy and safety outcomes.

Mycophenolate (CellCept, Myfortic) has replaced azathioprine (Imuran) in conventional maintenance immunosuppressant regimens because it is less likely than azathioprine to induce severe bone marrow depression. Other antiproliferatives, such as everolimus (Zortress) and sirolimus (Rapamune), are finding their niche in transplant immunosuppression and can be used to decrease the dose and, therefore, the potential for adverse effects with other drugs such as calcineurin inhibitors.

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